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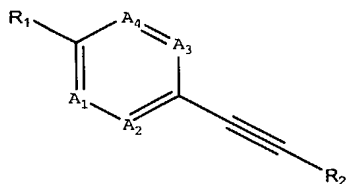
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(54) **Title:** HETEROARYL-SUBSTITUTED ALKYNE COMPOUNDS AND METHOD OF USE



(I)

(57) **Abstract:** The present invention comprises a new class of compounds useful for the prophylaxis and treatment of protein kinase mediated diseases, including inflammation, cancer and related conditions. The compounds have a general Formula I: wherein A₁, A₂, A₃, A₄, R₁ and R₂ are defined herein. Accordingly, the invention also comprises pharmaceutical compositions comprising the compounds of the invention, methods for the prophylaxis and treatment of kinase mediated diseases using the compounds and compositions of the invention, and intermediates and processes useful for the preparation of compounds of the invention.

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HETEROARYL-SUBSTITUTED ALKYNE COMPOUNDS AND METHOD OF USE

This application claims the benefit of U.S.
Provisional Application No. 60/620,100 filed October 18,
5 2004, which is incorporated by reference herein.

FIELD OF THE INVENTION

The invention generally relates to the field of
pharmaceutical agents and, more specifically, to compounds,
intermediates, methods for making the compounds and
10 intermediates, compositions, uses and methods for modulating
protein kinases and for treating protein kinase-mediated
diseases.

BACKGROUND OF THE INVENTION

Protein kinases represent a large family of enzymes,
15 which catalyze the phosphorylation of target protein
substrates. The phosphorylation is usually a transfer
reaction of a phosphate group from ATP to the protein
substrate. Common points of attachment for the phosphate
group to the protein substrate include, for example, a
20 tyrosine, serine or threonine residue. For example, protein
tyrosine kinases (PTKs) are enzymes, which catalyze the
phosphorylation of specific tyrosine residues in cellular
proteins. Examples of kinases in the protein kinase family
include, without limitation, abl, Akt, bcr-abl, Blk, Brk,
25 Btk, c-kit, c-Met, c-src, c-fms, CDK1, CDK2, CDK3, CDK4,
CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, cRaf1, CSF1R, CSK,
EGFR, ErbB2, ErbB3, ErbB4, Erk, Fak, fes, FGFR1, FGFR2,
FGFR3, FGFR4, FGFR5, Fgr, flt-1, Fps, Frk, Fyn, Hck, IGF-1R,
INS-R, Jak, KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2,
30 ros, Tie, Tie-2, TRK, Yes, and Zap70. Due to their activity
in numerous cellular processes, protein kinases have emerged
as important therapeutic targets.

Protein kinases play a central role in the regulation
and maintenance of a wide variety of cellular processes and
35 cellular function. For example, kinase activity acts as

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molecular switches regulating cell proliferation, activation, and/or differentiation. Uncontrolled or excessive kinase activity has been observed in many disease states including benign and malignant proliferation disorders as well as diseases resulting from inappropriate activation of the immune system (autoimmune disorders), allograft rejection, and graft vs host disease. In addition, endothelial cell specific receptor PTKs, such as VEGF-2 and Tie-2, mediate the angiogenic process and are involved in supporting the progression of cancers and other diseases involving uncontrolled vascularization.

Angiogenesis is the process of developing new blood vessels, particularly capillaries, from pre-existing vasculature and is an essential component of embryogenesis, normal physiological growth, repair, and tumor expansion. Angiogenesis remodels small vessels into larger conduit vessels, a physiologically important aspect of vascular growth in adult tissues. Vascular growth is required for beneficial processes such as tissue repair, wound healing, recovery from tissue ischemia and menstrual cycling.

Certain diseases and/or pathological conditions develop as a result of, or are known to be associated with, the regulation and/or deregulation of angiogenesis. For example, ocular neovascularisation such as retinopathies (including diabetic retinopathy), age-related macular degeneration, psoriasis, hemangioblastoma, hemangioma, and arteriosclerosis have been found to be caused, in part, due the loss of regulation and/or maintenance of vascular growth. Inflammatory diseases such as a rheumatoid or rheumatic inflammatory disease, and especially arthritis (including rheumatoid arthritis) where new capillary blood vessels invade the joint and destroy cartilage, have been associated with angiogenesis. In addition, chronic inflammatory disorders such as chronic asthma, arterial or

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post-transplantational atherosclerosis, endometriosis, and neoplastic diseases including so-called solid tumors and liquid tumors (for example, leukemias), have been found to be linked to the regulation and control of angiogenesis.

5 The involvement of angiogenesis in major diseases has led to the identification and development of various targets for inhibiting angiogenesis. These targets relate to various receptors, enzymes, and other proteins in the angiogenic process or cascade of events leading to
10 angiogenesis, such as, for example, activation of endothelial cells by an angiogenic signal, synthesis and release of degradative enzymes, endothelial cell migration, proliferation of endothelial cells, and formation of capillary tubules.

15 One target identified in the cascade of events leading to angiogenesis is the Tie receptor family. The Tie-1 and Tie-2 receptors are single-transmembrane, tyrosine kinase receptors (Tie stands for tyrosine kinase receptors with immunoglobulin and EGF homology domains). Tie-2 is an
20 endothelial cell specific receptor tyrosine kinase, which is involved in angiogenic processes, such as vessel branching, sprouting, remodeling, maturation and stability. Tie-2 is the first mammalian receptor for which both agonist
25 ligand(s) (for example, Angiopoietin-1 ("Ang1") which binds to and stimulates phosphorylation and signal transduction of Tie-2), and context dependent agonist/antagonist ligand(s) (for example, Angiopoietin-2 ("Ang2")) have been identified. Knock out and transgenic manipulation of the expression of Tie-2 and its ligands indicates that tight spacial and
30 temporal control of Tie-2 signaling is important for the proper development of new vascularization.

Biological models suggest that the stimulation of Tie-2 by the Ang1 ligand is directly involved in the branching, sprouting and outgrowth of new vessels, and recruitment and

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interaction of periendothelial support cells important in maintaining vessel integrity and inducing quiescence. The absence of Ang1 stimulation of Tie-2 or the inhibition of Tie-2 autophosphorylation by Ang2, which is produced at high
5 levels at sites of vascular regression, may cause a loss in vascular structure and matrix contacts resulting in endothelial death, especially in the absence of growth/survival stimuli.

Recently, upregulation of Tie-2 expression has been
10 found in the vascular synovial pannus of arthritic joints of humans, consistent with the role in inappropriate neovascularization. This finding suggests that Tie-2 plays a role in the progression of rheumatoid arthritis. Point mutations producing constitutively activated forms of Tie-2
15 have been identified in association with human venous malformation disorders. Tie-2 inhibitors would, therefore, be useful in treating such disorders, as well as in other instances of improper neovasacularization. However, with the recent recognition of Ang3 and Ang4 as additional Tie-2
20 binding ligands, targeting a Tie-2 ligand-receptor interaction as an anti-angiogenic therapeutic approach is less favorable. Accordingly, a Tie-2 receptor kinase inhibition approach has become the strategy of choice.

Angiogenesis is regarded as an absolute prerequisite
25 for tumors that grow beyond a diameter of about 1-2 mm. Up to this size, oxygen and nutrients may be supplied to the tumor cells by diffusion. Every tumor, regardless of its origin and its cause, is thus dependent on angiogenesis for its growth after it has reached a certain size.

30 Three principal mechanisms play an important part in the activity of angiogenesis inhibitors against tumors: 1) Inhibition of the growth of vessels, especially capillaries, into vascular resting tumors, with the result that there is no net tumor growth owing to the balance that is achieved

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between cell death and proliferation; 2) Prevention of the migration of tumor cells owing to the absence of blood flow to and from tumors; and 3) Inhibition of endothelial cell proliferation, thus avoiding the paracrine growth-stimulating effect exerted on the surrounding tissue by the endothelial cells which normally line the vessels. See R. Connell and J. Beebe, *Exp. Opin. Ther. Patents*, 11:77-114 (2001).

The inhibition of vascular growth in this context has also shown beneficial effects in preclinical animal models. For example, inhibition of angiogenesis by blocking vascular endothelial growth factor or its receptor has resulted in inhibition of tumor growth and in retinopathy. Also, the development of pathological pannus tissue in rheumatoid arthritis involves angiogenesis and might be blocked by inhibitors of angiogenesis.

The ability to stimulate vascular growth has potential utility for treatment of ischemia-induced pathologies such as myocardial infarction, coronary artery disease, peripheral vascular disease, and stroke. The sprouting of new vessels and/or the expansion of small vessels in ischemic tissues prevents ischemic tissue death and induces tissue repair. Regulating angiogenesis by inhibiting certain recognized pathways in this process would, therefore, be useful in treating diseases, such as ocular neovascularization, including retinopathy, age-related macular degeneration, psoriasis, hemangioblastoma, hemangioma, arteriosclerosis, inflammatory disease rheumatoid arthritis, chronic inflammatory disorders such as chronic asthma, arterial or post-transplantational atherosclerosis, endometriosis, and neoplastic diseases such as leukemias, otherwise known to be associated with deregulated angiogenesis. Treatment of malaria and related viral diseases may also be mediated by HGF and cMet.

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Recent work on the relationship between inhibition of angiogenesis and the suppression or reversion of tumor progression shows great promise in the treatment of cancer (Nature, 390:404-407 (1997)), especially the use of multiple
5 angiogenesis inhibitors compared to the effect of a single inhibitor.

Non-receptor tyrosine kinases represent a collection of cellular enzymes, which lack extracellular activity and transmembrane sequences. Examples of non-receptor tyrosine
10 kinases identified include over twenty-four individual kinases, comprising eleven (11) subfamilies (Src, Frk, Btk, Csk, Abl, Zap70, Fes/Fps, Fak, jak, Ack, and LIMK). Src is thought to be the largest family including Src, Lck, Fyn(B), Fyn(T), Lyn, Yes, Hck, Fgr and Blk (for review see: Bolen,
15 JB, and Brugge, JS Annu. Rev. Immunol, 15, 371, 1997). The Src subfamily has been linked to oncogenesis and immune responses (See Bohlen, Oncogene, 8:2025-2031, 1993). These kinases have also been found to be involved in cellular
20 signaling pathways in numerous pathogenic conditions, including cancer, psoriasis, and other hyper-proliferative disorders or hyper-immune responses. Thus, it would be useful to inhibit the activity of non-receptor kinases as well.

Members of the Src-family of tyrosine kinases, in
25 particular, have been shown to be important in cell signal transduction as it relates to inflammatory response and inflammation-related conditions. Gene disruption studies suggest that inhibition of some members of the src family of kinases would potentially lead to a therapeutic benefit.
30 Src(-/-) mice have abnormalities in bone remodeling or osteopetrosis (Soriano, P. Cell 1991, 64, 693), suggesting that inhibition of this kinase might be useful in diseases of bone resorption, such as osteoporosis. Lck(-/-) mice have defects in T cell maturation and activation (Anderson,

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SJ et al. Adv. Immunol. 1994, 56, 151), suggesting that inhibition of this kinase might be useful in diseases of T cell mediated inflammation. In addition, human patients have been identified with mutations affecting Lck kinase activity (Goldman, FD et al. J. Clin. Invest. 1998, 102, 421). These patients suffer from a severe combined immunodeficiency disorder (SCID).

T cells play a pivotal role in the regulation of immune responses and are important for establishing immunity to pathogens. In addition, T cells are often activated during inflammatory autoimmune diseases, such as rheumatoid arthritis, inflammatory bowel disease, type I diabetes, multiple sclerosis, Sjogren's disease, myasthenia gravis, psoriasis, and lupus. T cell activation is also an important component of transplant rejection, allergic reactions, and asthma.

T cells are activated by specific antigens through the T cell receptor (TCR), which is expressed on the cell surface. This activation triggers a series of intracellular signaling cascades mediated by enzymes expressed within the cell (Kane, LP et al. Current Opinion in Immunol. 12, 242, 2000). These cascades lead to gene regulation events that result in the production of cytokines, like interleukin-2 (IL-2). IL-2 is a necessary cytokine in T cell activation, leading to proliferation and amplification of specific immune responses.

Src-family kinases are also important for signaling downstream of other immune cell receptors. Fyn, like Lck, is involved in TCR signaling in T cells (Appleby, MW et al. Cell, 70, 751, 1992). Hck and Fgr are involved in Fcγ receptor signaling leading to neutrophil activation (Vicentini, L. et al. J. Immunol. 2002, 168, 6446). Lyn and Src also participate in Fcγ receptor signaling leading to release of histamine and other allergic mediators (Turner,

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H. and Kinet, J-P Nature 1999, 402, B24). These findings suggest that Src family kinase inhibitors may be useful in treating allergic diseases and asthma.

Src kinases are also activated in tumors including
5 sarcoma, melanoma, breast, and colon cancers suggesting that Src kinase inhibitors may be useful anti-cancer agents (Abram, CL and Courtneidge, SA Exp. Cell Res., 254, 1, 2000). Src kinase inhibitors have also been reported to be effective in an animal model of cerebral ischemia (R. Paul
10 et al. Nature Medicine, 7, 222, 2001), suggesting that Src kinase inhibitors may be effective at limiting brain damage following stroke.

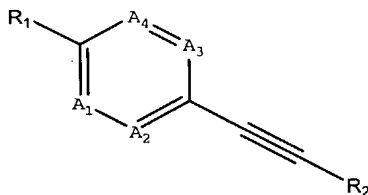
Many classes of compounds have been disclosed to modulate or, more specifically, inhibit kinase activity for
15 use to treat kinase-related conditions or other disorders. For example, the PCT publication, WO 01/81311, published on November 1, 2001, describes substituted benzoic acid amides and use thereof for the inhibition of angiogenesis; U.S. Patent No 6,440,965, issued August 27, 2002, describes
20 substituted pyrimidine derivatives and their use in the treatment of neurodegenerative or neurological disorders of the central nervous system; PCT publication, WO 02/08205, published on January 13, 2001, describes substituted pyrimidines having neurotrophic activity; PCT publication,
25 WO 03/014111, published on February 20, 2003, describes arylpiperazines and arylpiperidines and their use as metalloproteinase inhibiting agents; PCT publication, WO 03/024448, published on March 27, 2003, describes compounds as inhibitors of histone deacetylase enzymatic activity; PCT
30 publication, WO 04/058776, published on July 15, 2004, describes compounds which possess anti-angiogenic activity; and PCT publication, WO 04/062601, published on July 29, 2004, describes compounds as anti-bacterial agents for

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generally treating infections caused by gram-negative bacteria.

BRIEF DESCRIPTION OF THE INVENTION

5 The present invention provides new heteroaryl-substituted alkyne compounds useful in treating pathological conditions and/or disease states related to kinase activity. Particularly, the compounds are useful for treating various diseases, such as cancer, inflammation and related disorders and conditions including rheumatoid arthritis. The compounds are useful by virtue of their ability to regulate active angiogenesis, cell-signal transduction and related pathways, for example, through kinase modulation. The compounds provided by the invention, including stereoisomers, 10 tautomers, solvates, pharmaceutically acceptable salts, derivatives or prodrugs thereof, are defined by general Formula I



wherein A¹, A², A³, A⁴, R¹ and R² are as described below.

20 The invention also provides procedures for making compounds of Formula I, as well as intermediates useful in such procedures.

25 The compounds provided by the invention are capable of modulating various kinase activity. For example, in one embodiment, the compounds are capable of modulating one or both of Tie-2 or Lck kinase enzymes. In particular, the compounds are capable of inhibiting the activity of Tie-2, and Lck.

30 To this end, the invention further provides for the use of these compounds for therapeutic, prophylactic, acute and/or chronic treatment of Tie-2 and/or Lck kinase mediated

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diseases, such as those described herein. For example, the invention provides the use and preparation of a medicament, containing one or more of the compounds, useful to attenuate, alleviate, or treat disorders through inhibition of Tie-2 and/or Lck. These compounds are also useful in the treatment of an angiogenesis- or T-cell activation- or proliferation- mediated disease or condition. Accordingly, these compounds are useful in the manufacture of anti-cancer and anti-inflammation medicaments. In one embodiment, the invention provides a pharmaceutical composition comprising an effective dosage amount of a compound of Formula I in association with a least one pharmaceutically acceptable carrier, adjuvant or diluent.

Further, the invention provides a method of treating kinase mediated disorders, such as treating angiogenesis related or T-cell activation related disorders in a subject inflicted with, or susceptible to, such disorder. The method comprises administering to the subject an effective dosage amount of a compound of Formula I. In other embodiments, the invention provides methods of reducing tumor size, blood flow to and from a tumor, and treating or alleviating various inflammatory responses, including arthritis, organ transplantation or rejection, and many others as described herein.

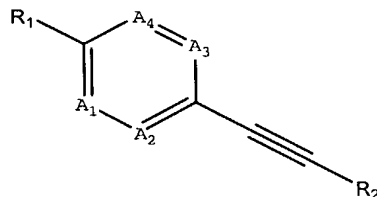
The foregoing merely summarizes certain aspects of the invention and is not intended, nor should it be construed, as limiting the invention in any way. All patents and other publications recited herein are hereby incorporated by reference in their entirety.

DETAILED DESCRIPTION OF THE INVENTION

In one embodiment of the invention, heteroaryl-substituted alkyne compounds useful for treating

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angiogenesis- and/or T-cell proliferation-related disorders, including cancer and inflammation are provided. The compounds, including stereoisomers, tautomers, solvates, pharmaceutically acceptable salts, derivatives or prodrugs thereof, are defined by general Formula I:



I

wherein

10 A^1 is CR^3 or N;

A^2 is CR^4 or N;

A^3 is CR^5 or N;

A^4 is CR^6 or N;

provided that at least one of A^1 , A^2 , A^3 and A^4 is N and
 15 no more than three of A^1 , A^2 , A^3 and A^4 are N;

R^1 is NR^7R^7 , NR^7R^8 , SR^7 , OR^8 ; SR^8 , $C(O)R^7$, $OC(O)R^7$, $COOR^7$, $C(O)R^8$, $OC(O)R^8$, $COOR^8$, $C(O)NR^7R^7$, $C(S)NR^7R^7$, $NR^7C(O)R^7$, $NR^7C(S)R^7$, $NR^7C(O)NR^7R^7$, $NR^7C(S)NR^7R^7$, $NR^7(COOR^7)$, $OC(O)NR^7R^7$, $C(O)NR^7R^8$, $C(S)NR^7R^8$, $NR^7C(O)R^8$, $NR^7C(S)R^8$, $NR^7C(O)NR^7R^8$,
 20 $NR^7C(S)NR^7R^8$, $NR^7(COOR^8)$, $OC(O)NR^7R^8$, $S(O)_2NR^7R^7$, $NR^7S(O)_2NR^7R^7$, $NR^7S(O)_2R^7$, $S(O)_2R^8$, $S(O)_2NR^7R^8$, $NR^7S(O)_2NR^7R^8$ or $NR^7S(O)_2R^8$;

R^2 is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of
 25 carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, wherein said ring system is substituted independently with one or more substituents of R^{10} , R^{11} , R^{15} , $NR^{10}R^{10}$, $NR^{10}R^{11}$, OR^{10} ,
 30 SR^{10} , OR^{11} , SR^{11} , $C(O)R^{10}$, $C(S)R^{10}$, $C(NCN)R^{10}$, $C(O)R^{11}$, $C(S)R^{11}$,

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$C(NCN)R^{11}$, $C(O)C(O)R^{10}$, $OC(O)R^{10}$, $COOR^{10}$, $C(O)SR^{10}$, $C(O)C(O)R^{11}$,
 $OC(O)R^{11}$, $COOR^{11}$, $C(O)SR^{11}$, $C(O)NR^{10}R^{10}$, $C(S)NR^{10}R^{10}$, $C(O)NR^{10}R^{11}$,
 $C(S)NR^{10}R^{11}$, $OC(O)NR^{10}R^{11}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)R^{11}$, $NR^{10}C(S)R^{10}$,
 $NR^{10}C(S)R^{11}$, $NR^{10}C(O)NR^{10}R^{10}$, $NR^{10}C(O)NR^{10}R^{11}$, $NR^{10}C(S)NR^{10}R^{10}$,
5 $NR^{10}C(S)NR^{10}R^{11}$, $NR^{10}(COOR^{10})$, $NR^{10}(COOR^{11})$, $NR^{10}C(O)C(O)R^{10}$,
 $NR^{10}C(O)C(O)R^{11}$, $NR^{10}C(O)C(O)NR^{10}R^{11}$, $S(O)_2R^{10}$, $S(O)_2R^{11}$,
 $S(O)_2NR^{10}R^{10}$, $S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2R^{10}$ or
 $NR^{10}S(O)_2R^{11}$, provided that at least one substituent on said
ring system is $C(O)_2R^{10}$, $C(O)_2R^{11}$, $C(O)C(O)R^{10}$, $OC(O)R^{10}$,
10 $COOR^{10}$, $C(O)SR^{10}$, $C(O)C(O)R^{11}$, $OC(O)R^{11}$, $COOR^{11}$, $C(O)SR^{11}$,
 $C(O)NR^{10}R^{10}$, $C(S)NR^{10}R^{10}$, $C(O)NR^{10}R^{11}$, $C(S)NR^{10}R^{11}$, $OC(O)NR^{10}R^{11}$,
 $NR^{10}R^{11}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)R^{11}$, $NR^{10}C(S)R^{10}$, $NR^{10}C(S)R^{11}$,
 $NR^{10}C(O)NR^{10}R^{10}$, $NR^{10}C(O)NR^{10}R^{11}$, $NR^{10}C(S)NR^{10}R^{10}$, $NR^{10}C(S)NR^{10}R^{11}$,
 $NR^{10}(COOR^{10})$, $NR^{10}(COOR^{11})$, $NR^{10}C(O)C(O)R^{10}$, $NR^{10}C(O)C(O)R^{11}$,
15 $NR^{10}C(O)C(O)NR^{10}R^{11}$, $S(O)_2R^{10}$, $S(O)_2R^{11}$, $S(O)_2NR^{10}R^{10}$, $S(O)_2NR^{10}R^{11}$,
 $NR^{10}S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2R^{10}$ or $NR^{10}S(O)_2R^{11}$;

R^3 is H, halo, haloalkyl, NO_2 , CN, OR^7 , SR^7 , NR^7R^7 ,
 NR^7R^8 , $C(O)R^7$, $COOR^7$, $C(O)NR^7R^7$, $C(O)NR^7R^8$, $NR^7C(O)NR^7R^7$,
 $NR^7C(O)NR^7R^8$, $OC(O)NR^7R^8$, $S(O)_2R^7$, $S(O)_2NR^7R^7$, $S(O)_2NR^7R^8$,
20 $NR^7S(O)_2R^7$, $NR^7S(O)_2R^8$, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl,
 C_{3-10} -cycloalkyl or C_{4-10} -cycloalkenyl, each of the C_{1-10} -alkyl,
 C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl and C_{4-10} -
cycloalkenyl optionally comprising 1-4 heteroatoms selected
from N, O and S and optionally substituted with 1-5
25 substituents of R^8 or R^9 ;

alternatively R^1 and R^3 taken together with the atoms to
which they are attached form a partially or fully
unsaturated 5- or 6-membered ring of carbon atoms optionally
including 1-3 heteroatoms selected from O, N, or S, and the
30 ring optionally substituted independently with 1-5
substituents of R^8 or R^9 ;

R^4 is H, halo, haloalkyl, NO_2 , CN, NR^7R^7 , OR^7 ; SR^7 ,
 $C(O)R^7$, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -
cycloalkyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -

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alkynyl and C₃₋₁₀-cycloalkyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-5 substituents of R⁹;

alternatively R³ and R⁴ taken together with the atoms to which they are attached form a partially or fully unsaturated 5- or 6-membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-3 substituents of R⁸ or R⁹

10 R⁵ is H, halo, haloalkyl, NO₂, CN, NR⁷R⁷, OR⁷; SR⁷, C(O)R⁷, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-cycloalkyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl and C₃₋₁₀-cycloalkyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-5 substituents of R⁹;

15 R⁶ is H, halo, haloalkyl, NO₂, CN, SR⁷, OR⁷, C(O)R⁷, COOR⁷, OC(O)R⁷, NR⁷R⁷, NR⁷R⁸, C(O)NR⁷R⁷, C(O)NR⁷R⁸, NR⁷C(O)R⁷, NR⁷C(O)NR⁷R⁸, S(O)NR⁷R⁸, S(O)₂NR⁷R⁸, NR⁷S(O)NR⁷R⁸, NR⁷S(O)₂NR⁷R⁸, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl or C₄₋₁₀-cycloalkenyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl and C₄₋₁₀-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-5 substituents of R⁸ or R⁹;

alternatively R¹ and R⁶ taken together with the atoms to which they are attached form a partially or fully unsaturated 5- or 6-membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-5 substituents of R⁸ or R⁹;

25 alternatively R⁵ and R⁶ taken together with the atoms to which they are attached form a partially or fully unsaturated 5- or 6-membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the

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ring optionally substituted independently with 1-3 substituents of R^8 or R^9 ;

R^7 is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl or C_{4-10} -cycloalkenyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl and C_{4-10} -cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-5 substituents of NR^8R^9 , NR^9R^9 , OR^8 , SR^8 , OR^9 , SR^9 , $C(O)R^8$, $OC(O)R^8$, $COOR^8$, $C(O)R^9$, $OC(O)R^9$, $COOR^9$, $C(O)NR^8R^9$, $C(O)NR^9R^9$, $NR^9C(O)R^8$, $NR^9C(O)R^9$, $NR^9C(O)NR^8R^9$, $NR^9C(O)NR^9R^9$, $NR^9(COOR^8)$, $NR^9(COOR^9)$, $OC(O)NR^8R^9$, $OC(O)NR^9R^9$, $S(O)_2R^8$, $S(O)_2NR^8R^9$, $S(O)_2R^9$, $S(O)_2NR^9R^9$, $NR^9S(O)_2NR^8R^9$, $NR^9S(O)_2NR^9R^9$, $NR^9S(O)_2R^8$, $NR^9S(O)_2R^9$, R^8 or R^9 ;

R^8 is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein said ring system is optionally substituted independently with 1-5 substituents of R^9 , oxo, NR^9R^9 , OR^9 , SR^9 , $C(O)R^9$ or a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of R^9 ;

alternatively, R^7 and R^8 taken together form a saturated or partially or fully unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and said ring optionally substituted independently with 1-5 substituents of R^9 ;

R^9 is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , acetyl, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl, C_{1-10} -thioalkoxyl or a saturated or partially or

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fully unsaturated 5-8 membered monocyclic or a 6-12 membered bicyclic, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, wherein each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl and ring of said ring system is optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamine, dimethylamine, ethylamine, diethylamine, propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;

R¹⁰ is H, halo, haloalkyl, CN, NO₂, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl or C₄₋₁₀-cycloalkenyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl and C₄₋₁₀-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-5 substituents of R¹¹, R¹² or R¹⁶, NR¹¹R¹², NR¹²R¹², OR¹¹, SR¹¹, OR¹², SR¹², C(O)R¹¹, OC(O)R¹¹, COOR¹¹, C(O)R¹², OC(O)R¹², COOR¹², C(O)NR¹¹R¹², NR¹²C(O)R¹¹, C(O)NR¹²R¹², NR¹²C(O)R¹², NR¹²C(O)NR¹¹R¹², NR¹²C(O)NR¹²R¹², NR¹²(COOR¹¹), NR¹²(COOR¹²), OC(O)NR¹¹R¹², OC(O)NR¹²R¹², S(O)₂R¹¹, S(O)₂R¹², S(O)₂NR¹¹R¹², S(O)₂NR¹²R¹², NR¹²S(O)₂NR¹¹R¹², NR¹²S(O)₂NR¹²R¹², NR¹²S(O)₂R¹¹, NR¹²S(O)₂R¹², NR¹²S(O)₂R¹¹ or NR¹²S(O)₂R¹²;

R¹¹ is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein each ring of said ring system is optionally

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substituted independently with 1-5 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

alternatively, R^{10} and R^{11} taken together form a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-5 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which is optionally substituted independently with 1-5 substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} , SR^{14} , OR^{15} , SR^{15} , $C(O)R^{14}$, $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$, $C(O)NR^{15}R^{15}$, $NR^{14}C(O)R^{14}$, $NR^{15}C(O)R^{14}$, $NR^{14}C(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(O)NR^{14}R^{15}$, $NR^{15}C(O)NR^{15}R^{15}$, $NR^{15}(COOR^{14})$, $NR^{15}(COOR^{15})$, $OC(O)NR^{14}R^{15}$, $OC(O)NR^{15}R^{15}$, $S(O)_2R^{14}$, $S(O)_2R^{15}$, $S(O)_2NR^{14}R^{15}$, $S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2NR^{14}R^{15}$, $NR^{15}S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2R^{14}$ or $NR^{15}S(O)_2R^{15}$;

R^{14} is a partially or fully saturated or unsaturated 5-8 membered or a saturated or partially or fully unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein said ring system is optionally substituted independently with 1-5 substituents of R^{15} or R^{16} ;

R^{15} is H or C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkoxyl, each of which is optionally substituted independently with 1-5 substituents of R^{16} ;

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R¹⁶ is H, halo, haloalkyl, CN, OH, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl;

and provided that (1) when said at least one substituent on said R² ring system is C(O)NR¹⁰R¹⁰ or C(O)NR¹⁰R¹¹, then R¹⁰ and R¹¹, independently, are not -CH₂-L-Q, wherein L is -O-, -NH-, -NHC(O)-, -NHC(O)N-, -NHC(=NH)N- or -CO₂- and Q is H, substituted or unsubstituted C₁₋₆alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteraryl or C₁₋₆alkyl substituted with aryl, heterocyclyl or heteroaryl; or

(2) when said R² is a phenyl ring substituted with C(O)NR¹⁰R¹⁰ or C(O)NR¹⁰R¹¹ meta to the alkynyl group of Formula I, then either (a) R¹ is not halogen, C₁₋₆alkyl, C₁₋₆alkoxyl or hydroxyl or (b) where R¹ and R³ taken together with the atoms to which they are attached form a partially or fully unsaturated 5- or 6-membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, said ring is not substituted with halogen, C₁₋₆alkyl, C₁₋₆alkoxyl or hydroxyl substituents.

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In another embodiment, the compounds of Formula I include N as A¹, in conjunction with any of the above or below embodiments.

5 In another embodiment, the compounds of Formula I include N as A⁴, in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I include N, independently, as both A¹ and A⁴, in conjunction with any of the above or below embodiments.

10 In another embodiment, the compounds of Formula I include compounds wherein A¹ is N, A² is CR⁴, A³ is CR⁵ and A⁴ is CR⁶, in conjunction with any of the above or below embodiments.

15 In another embodiment, the compounds of Formula I include compounds wherein A¹ is CR³, A² is CR⁴, A³ is CR⁵ and A⁴ is N, in conjunction with any of the above or below embodiments.

20 In another embodiment, the compounds of Formula I include compounds wherein each of A² and A³, independently, is N, A¹ is CR³ and A⁴ is CR⁶, in conjunction with any of the above or below embodiments.

25 In another embodiment, the compounds of Formula I include compounds wherein each of A¹ and A², independently, is N, A³ is CR⁵ and A⁴ is CR⁶, in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I include compounds wherein each of A¹ and A⁴, independently, is N, A² is CR⁴ and A³ is CR⁵, in conjunction with any of the above or below embodiments.

30 In another embodiment, the compounds of Formula I include N as A¹, N as A⁴, and a substituted 5-6 membered monocyclic aryl or heteroaryl ring system, or a 8-12 membered bicyclic aryl or heteroaryl ring system, said ring system including 1-3 heteroatoms if monocyclic or 1-6

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heteroatoms if bicyclic, said heteroatoms selected from O, N and S as R³, in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I include phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl as the substituted ring system of R² in the embodiment above, in conjunction with any of the above or below embodiments.

In another embodiment, the compounds of Formula I in the embodiment immediately above include C(O)R¹⁰, COOR¹⁰, C(O)R¹¹, COOR¹¹, C(O)NR¹⁰R¹⁰, C(S)NR¹⁰R¹⁰, C(O)NR¹⁰R¹¹, C(S)NR¹⁰R¹¹, NR¹⁰R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(S)R¹⁰, NR¹⁰C(O)R¹¹, NR¹⁰C(S)R¹¹, NR¹⁰C(O)NR¹⁰R¹⁰, NR¹⁰C(O)NR¹⁰R¹¹, NR¹⁰C(S)NR¹⁰R¹⁰, NR¹⁰C(S)NR¹⁰R¹¹, NR¹⁰(COOR¹⁰), NR¹⁰(COOR¹¹), S(O)₂NR¹⁰R¹⁰, S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂R¹⁰ or NR¹⁰S(O)₂R¹¹ as a substituent on R², taken in conjunction with any of the above or below embodiments.

In another embodiment, the compounds are generally defined by Formula I above, wherein

A¹ and A⁴, independently, are N;

A² is CR⁴;

A³ is CR⁵;

R¹ is NR⁷R⁷, NR⁷R⁸, SR⁷, OR⁸, SR⁸, C(O)R⁷, OC(O)R⁷, COOR⁷, C(O)R⁸, OC(O)R⁸, COOR⁸, C(O)NR⁷R⁷, C(S)NR⁷R⁷, NR⁷C(O)R⁷, NR⁷C(S)R⁷, NR⁷C(O)NR⁷R⁷, NR⁷C(S)NR⁷R⁷, NR⁷(COOR⁷), OC(O)NR⁷R⁷, C(O)NR⁷R⁸, C(S)NR⁷R⁸, NR⁷C(O)R⁸, NR⁷C(S)R⁸, NR⁷C(O)NR⁷R⁸, NR⁷C(S)NR⁷R⁸, NR⁷(COOR⁸), OC(O)NR⁷R⁸, S(O)₂R⁷, S(O)₂NR⁷R⁷, NR⁷S(O)₂NR⁷R⁷, NR⁷S(O)₂R⁷, S(O)₂R⁸, S(O)₂NR⁷R⁸, NR⁷S(O)₂NR⁷R⁸ or NR⁷S(O)₂R⁸;

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R^2 is a phenyl, naphthyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, phthalazinyl, aza-phthalazinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, thiadiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl ring system, said ring system substituted independently with 1-5 substituents of R^{10} , R^{11} , R^{15} , $NR^{10}R^{10}$, $NR^{10}R^{11}$, OR^{10} , SR^{10} , OR^{11} , SR^{11} , $C(O)R^{10}$, $C(S)R^{10}$, $C(NCN)R^{10}$, $C(O)R^{11}$, $C(S)R^{11}$, $C(NCN)R^{11}$, $C(O)C(O)R^{10}$, $OC(O)R^{10}$, $COOR^{10}$, $C(O)SR^{10}$, $C(O)C(O)R^{11}$, $OC(O)R^{11}$, $COOR^{11}$, $C(O)SR^{11}$, $C(O)NR^{10}R^{10}$, $C(S)NR^{10}R^{10}$, $C(O)NR^{10}R^{11}$, $C(S)NR^{10}R^{11}$, $OC(O)NR^{10}R^{11}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)R^{11}$, $NR^{10}C(S)R^{10}$, $NR^{10}C(S)R^{11}$, $NR^{10}C(O)NR^{10}R^{10}$, $NR^{10}C(O)NR^{10}R^{11}$, $NR^{10}C(S)NR^{10}R^{10}$, $NR^{10}C(S)NR^{10}R^{11}$, $NR^{10}(COOR^{10})$, $NR^{10}(COOR^{11})$, $NR^{10}C(O)C(O)R^{10}$, $NR^{10}C(O)C(O)R^{11}$, $NR^{10}C(O)C(O)NR^{10}R^{11}$, $S(O)_2R^{10}$, $S(O)_2R^{11}$, $S(O)_2NR^{10}R^{10}$, $S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2R^{10}$ or $NR^{10}S(O)_2R^{11}$, provided that (1) one substituent is $C(O)R^{10}$, $COOR^{10}$, $C(O)R^{11}$, $COOR^{11}$, $C(O)NR^{10}R^{10}$, $C(S)NR^{10}R^{10}$, $C(O)NR^{10}R^{11}$, $C(S)NR^{10}R^{11}$, $NR^{10}R^{11}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(S)R^{10}$, $NR^{10}C(O)R^{11}$, $NR^{10}C(S)R^{11}$, $NR^{10}C(S)NR^{10}R^{10}$, $NR^{10}C(S)NR^{10}R^{11}$, $S(O)_2NR^{10}R^{10}$, $S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2R^{10}$ or $NR^{10}S(O)_2R^{11}$;

R^4 is H, halo, haloalkyl, NO_2 , CN, NR^7R^7 , OR^7 , SR^7 , $C(O)R^7$, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl and C_{3-10} -cycloalkyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-3 substituents of R^9 ;

R^5 is H, halo, haloalkyl, NO_2 , CN, NR^7R^7 , OR^7 , SR^7 , $C(O)R^7$, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl and C_{3-10} -cycloalkyl optionally comprising 1-4

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heteroatoms selected from N, O and S and optionally substituted with 1-3 substituents of R⁹;

R⁷ is H, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl or C₄₋₁₀-cycloalkenyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl and C₄₋₁₀-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-3 substituents of NR⁸R⁹, NR⁹R⁹, OR⁸, SR⁸, OR⁹, SR⁹, C(O)R⁸, OC(O)R⁸, COOR⁸, C(O)R⁹, OC(O)R⁹, COOR⁹, C(O)NR⁸R⁹, C(O)NR⁹R⁹, NR⁹C(O)R⁸, NR⁹C(O)R⁹, NR⁹C(O)NR⁸R⁹, NR⁹C(O)NR⁹R⁹, NR⁹(COOR⁸), NR⁹(COOR⁹), OC(O)NR⁸R⁹, OC(O)NR⁹R⁹, S(O)₂R⁸, S(O)₂NR⁸R⁹, S(O)₂R⁹, S(O)₂NR⁹R⁹, NR⁹S(O)₂NR⁸R⁹, NR⁹S(O)₂NR⁹R⁹, NR⁹S(O)₂R⁸, NR⁹S(O)₂R⁹, R⁸ or R⁹;

R⁸ is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein said ring system is optionally substituted independently with 1-5 substituents of R⁹, oxo, NR⁹R⁹, OR⁹, SR⁹, C(O)R⁹ or a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and optionally substituted independently with 1-3 substituents of R⁹;

alternatively, R⁷ and R⁸ taken together form a saturated or partially or fully unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-3 substituents of R⁹;

R⁹ is H, halo, haloalkyl, CN, OH, NO₂, NH₂, acetyl, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl or a saturated or partially or

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fully unsaturated 5-8 membered monocyclic or a 6-12 membered bicyclic, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, wherein each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl and ring of said ring system is optionally substituted independently with 1-3 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamine, dimethylamine, ethylamine, diethylamine, propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;

R¹⁰ is H, halo, haloalkyl, CN, NO₂, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl or C₄₋₁₀-cycloalkenyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl and C₄₋₁₀-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-5 substituents of R¹¹, R¹² or R¹⁶, NR¹¹R¹², NR¹²R¹², OR¹¹, SR¹¹, OR¹², SR¹², C(O)R¹¹, OC(O)R¹¹, COOR¹¹, C(O)R¹², OC(O)R¹², COOR¹², C(O)NR¹¹R¹², NR¹²C(O)R¹¹, C(O)NR¹²R¹², NR¹²C(O)R¹², NR¹²C(O)NR¹¹R¹², NR¹²C(O)NR¹²R¹², NR¹²(COOR¹¹), NR¹²(COOR¹²), OC(O)NR¹¹R¹², OC(O)NR¹²R¹², S(O)₂R¹¹, S(O)₂R¹², S(O)₂NR¹¹R¹², S(O)₂NR¹²R¹², NR¹²S(O)₂NR¹¹R¹², NR¹²S(O)₂NR¹²R¹², NR¹²S(O)₂R¹¹, NR¹²S(O)₂R¹², NR¹²S(O)₂R¹¹ or NR¹²S(O)₂R¹²;

R¹¹ is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein each ring of said ring system is optionally

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substituted independently with 1-5 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

alternatively, R^{10} and R^{11} taken together form a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-5 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which is optionally substituted independently with 1-5 substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} ; SR^{14} , OR^{15} ; SR^{15} , $C(O)R^{14}$, $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$, $C(O)NR^{15}R^{15}$, $NR^{14}C(O)R^{14}$, $NR^{15}C(O)R^{14}$, $NR^{14}C(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(O)NR^{14}R^{15}$, $NR^{15}C(O)NR^{15}R^{15}$, $NR^{15}(COOR^{14})$, $NR^{15}(COOR^{15})$, $OC(O)NR^{14}R^{15}$, $OC(O)NR^{15}R^{15}$, $S(O)_2R^{14}$, $S(O)_2R^{15}$, $S(O)_2NR^{14}R^{15}$, $S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2NR^{14}R^{15}$, $NR^{15}S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2R^{14}$ or $NR^{15}S(O)_2R^{15}$;

R^{14} is a partially or fully saturated or unsaturated 5-8 membered or a saturated or partially or fully unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein each ring of said ring system is optionally substituted independently with 1-5 substituents of R^{15} or R^{16} ;

R^{15} is H or C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkoxyl, each of

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which is optionally substituted independently with 1-5 substituents of R^{16} ;

R^{16} is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO_2 , NH_2 , OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl;

and provided that (1) when said at least one substituent on said R^2 ring system is $C(O)NR^{10}R^{10}$ or $C(O)NR^{10}R^{11}$, then R^{10} and R^{11} , independently, are not $-CH_2-L-Q$ or $-C(C_{1-6}alkyl)(C_{1-6}alkyl)-L-Q$, wherein L is $-O-$, $-NH-$, $-NHC(O)-$, $-NHC(O)N-$, $-NHC(=NH)N-$ or $-CO_2-$ and Q is H, substituted or unsubstituted $C_{1-6}alkyl$, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteraryl or $C_{1-6}alkyl$ substituted with aryl, heterocyclyl or heteroaryl;

(2) where the sole substituent on said R^2 ring system is R^{10} , said substituent is not $C_1-alkyl-C(O)NR^{11}R^{12}$, $C_1-alkyl-NR^{12}C(O)R^{11}$, $C_1-alkyl-C(O)NR^{12}R^{12}$ or $C_1-alkyl-NR^{12}C(O)R^{12}$,

wherein the $C_1-alkyl$ portion is CH_2 or substituted with $C_{1-6}alkyl$ or cycloalkyl; or (3) when said R^2 is a phenyl ring substituted with $C(O)NR^{10}R^{10}$ or $C(O)NR^{10}R^{11}$ meta to the alkynyl group of Formula I, then either (a) R^1 is not halogen, $C_{1-6}alkyl$, $C_{1-6}alkoxyl$ or hydroxyl or (b) where R^1 and R^3 taken

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together with the atoms to which they are attached form a partially or fully unsaturated 5- or 6-membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, said ring is not substituted with halogen,
 5 C₁₋₆alkyl, C₁₋₆alkoxyl or hydroxyl substituents.

In another embodiment, the compounds of the embodiment immediately above, are generally defined by Formula I above, wherein R¹ is R⁷, NR⁷R⁷, NR⁷R⁸, SR⁷, C(O)R⁷, C(O)NR⁷R⁷, C(S)NR⁷R⁷, NR⁷C(O)R⁷, NR⁷C(S)R⁷, NR⁷C(O)NR⁷R⁷, NR⁷C(S)NR⁷R⁷,
 10 NR⁷(COOR⁷), C(O)NR⁷R⁸, C(S)NR⁷R⁸, NR⁷C(O)NR⁷R⁸, NR⁷C(S)NR⁷R⁸, S(O)₂R⁷, S(O)₂NR⁷R⁷, NR⁷S(O)₂NR⁷R⁷, NR⁷S(O)₂R⁷, S(O)₂NR⁷R⁸ or NR⁷S(O)₂NR⁷R⁸;

R² is a phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl,
 15 isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl ring system, said ring system substituted independently with 1-3 substituents of
 20 R¹⁰, R¹¹, R¹⁵, NR¹⁰R¹⁰, NR¹⁰R¹¹, OR¹⁰, SR¹⁰, OR¹¹, SR¹¹, C(O)R¹⁰, C(S)R¹⁰, C(NCN)R¹⁰, C(O)R¹¹, C(S)R¹¹, C(NCN)R¹¹, C(O)C(O)R¹⁰, OC(O)R¹⁰, COOR¹⁰, C(O)SR¹⁰, C(O)C(O)R¹¹, OC(O)R¹¹, COOR¹¹, C(O)SR¹¹, C(O)NR¹⁰R¹⁰, C(S)NR¹⁰R¹⁰, C(O)NR¹⁰R¹¹, C(S)NR¹⁰R¹¹, OC(O)NR¹⁰R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(O)R¹¹, NR¹⁰C(S)R¹⁰, NR¹⁰C(S)R¹¹,
 25 NR¹⁰C(O)NR¹⁰R¹⁰, NR¹⁰C(O)NR¹⁰R¹¹, NR¹⁰C(S)NR¹⁰R¹⁰, NR¹⁰C(S)NR¹⁰R¹¹, NR¹⁰(COOR¹⁰), NR¹⁰(COOR¹¹), NR¹⁰C(O)C(O)R¹⁰, NR¹⁰C(O)C(O)R¹¹, NR¹⁰C(O)C(O)NR¹⁰R¹¹, S(O)₂R¹⁰, S(O)₂R¹¹, S(O)₂NR¹⁰R¹⁰, S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂R¹⁰ or NR¹⁰S(O)₂R¹¹, provided that one substituent is C(O)R¹¹, COOR¹¹, C(O)NR¹⁰R¹¹, C(S)NR¹⁰R¹¹, NR¹⁰R¹¹,
 30 NR¹⁰C(O)R¹¹, NR¹⁰C(S)R¹¹, NR¹⁰C(O)NR¹⁰R¹¹, NR¹⁰C(S)NR¹⁰R¹¹, NR¹⁰(COOR¹¹), S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂NR¹⁰R¹¹ or NR¹⁰S(O)₂R¹¹;

R⁴ is H, halo, haloalkyl, NO₂, CN, NH₂, N-C₁₋₁₀-alkyl, N-C₁₋₁₀-dialkyl, O-C₁₋₁₀-alkyl, S-C₁₋₁₀-alkyl, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-cycloalkyl;

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R⁵ is H, halo, haloalkyl, NO₂, CN, NH₂, N-C₁₋₁₀-alkyl, N-C₁₋₁₀-dialkyl, O-C₁₋₁₀-alkyl, S-C₁₋₁₀-alkyl, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-cycloalkyl;

R⁷ is H, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-cycloalkyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl and C₃₋₁₀-cycloalkyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-3 substituents of NR⁸R⁹, NR⁹R⁸, OR⁸, SR⁸, OR⁹, SR⁹, C(O)R⁸, OC(O)R⁸, COOR⁸, C(O)R⁹, OC(O)R⁹, COOR⁹, C(O)NR⁸R⁹, C(O)NR⁹R⁸, NR⁹C(O)R⁸, NR⁹C(O)R⁹, NR⁹C(O)NR⁸R⁹, NR⁹C(O)NR⁹R⁸, NR⁹(COOR⁸), NR⁹(COOR⁹), OC(O)NR⁸R⁹, OC(O)NR⁹R⁸, S(O)₂R⁸, S(O)₂NR⁸R⁹, S(O)₂R⁹, S(O)₂NR⁹R⁸, NR⁹S(O)₂NR⁸R⁹, NR⁹S(O)₂NR⁹R⁸, NR⁹S(O)₂R⁸, NR⁹S(O)₂R⁹, R⁸ or R⁹;

R⁸ is a ring system of phenyl, naphthyl, pyridyl, pyrimidinyl, pyrrolidinyl, piperidinyl, piperazinyl, triazinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, tetrahydroquinazolinyl, tetrahydroisoquinazolinyl, morpholinyl, thiophenyl, furyl, dihydrofuryl, tetrahydrofuryl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl, said ring system optionally substituted independently with 1-3 substituents of R⁹, oxo, NR⁹R⁹, OR⁹, SR⁹, C(O)R⁹ or a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and optionally substituted independently with 1-3 substituents of R⁹;

alternatively, R⁷ and R⁸ taken together form a saturated or partially or fully unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-3 substituents of R⁹;

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R^9 is H, halo, haloalkyl, CN, OH, NO₂, NH₂, acetyl, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl or a ring system of phenyl, naphthyl, pyridyl, pyrimidinyl, pyrrolidinyl, piperidinyl, piperazinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, tetrahydroquinazolinyl, tetrahydroisoquinazolinyl, morpholinyl, thiophenyl, furyl, dihydrofuryl, tetrahydrofuryl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl and benzimidazolyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl and ring system optionally substituted independently with 1-3 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamine, dimethylamine, ethylamine, diethylamine, propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;

R^{10} is H, halo, haloalkyl, CN, NO₂, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl or C₄₋₁₀-cycloalkenyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl and C₄₋₁₀-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-5 substituents of R^{11} , R^{12} or R^{16} , NR¹¹R¹², NR¹²R¹², OR¹¹, SR¹¹, OR¹², SR¹², C(O)R¹¹, OC(O)R¹¹, COOR¹¹, C(O)R¹², OC(O)R¹², COOR¹², C(O)NR¹¹R¹², NR¹²C(O)R¹¹, C(O)NR¹²R¹², NR¹²C(O)R¹², NR¹²C(O)NR¹¹R¹², NR¹²C(O)NR¹²R¹², NR¹²(COOR¹¹), NR¹²(COOR¹²), OC(O)NR¹¹R¹², OC(O)NR¹²R¹², S(O)₂R¹¹, S(O)₂R¹², S(O)₂NR¹¹R¹², S(O)₂NR¹²R¹², NR¹²S(O)₂NR¹¹R¹², NR¹²S(O)₂NR¹²R¹², NR¹²S(O)₂R¹¹, NR¹²S(O)₂R¹², NR¹²S(O)₂R¹¹ or NR¹²S(O)₂R¹²;

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R^{11} is a ring system of phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, tetrahydroquinazolinyl, 5 tetrahydroisoquinazolinyl, morpholinyl, thiophenyl, furyl, dihydrofuryl, tetrahydrofuryl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl, said 10 ring system optionally substituted independently with 1-5 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

alternatively, R^{10} and R^{11} taken together form a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms 15 selected from O, N, or S, and the ring optionally substituted independently with 1-5 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which 20 is optionally substituted independently with 1-5 substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} ; SR^{14} , OR^{15} ; SR^{15} , $C(O)R^{14}$, $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$, 25 $C(O)NR^{15}R^{15}$, $NR^{14}C(O)R^{14}$, $NR^{15}C(O)R^{14}$, $NR^{14}C(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(O)NR^{14}R^{15}$, $NR^{15}C(O)NR^{15}R^{15}$, $NR^{15}(COOR^{14})$, $NR^{15}(COOR^{15})$, $OC(O)NR^{14}R^{15}$, $OC(O)NR^{15}R^{15}$, $S(O)_2R^{14}$, $S(O)_2R^{15}$, $S(O)_2NR^{14}R^{15}$, $S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2NR^{14}R^{15}$, $NR^{15}S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2R^{14}$ or $NR^{15}S(O)_2R^{15}$;

R^{14} is a partially or fully saturated or unsaturated 5-8 membered or a saturated or partially or fully unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if 30

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monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein each ring of said ring system is optionally substituted independently with 1-5 substituents of R¹⁵ or
5 R¹⁶;

R¹⁵ is H or C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl or C₁₋₁₀-thioalkoxyl, each of which is optionally substituted independently with 1-5
10 substituents of R¹⁶; and

R¹⁶ is H, halo, haloalkyl, CN, OH, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino,
15 oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic,
20 said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino,
25 ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

In another embodiment, the compounds of the embodiment immediately above, are generally defined by Formula I above, wherein R¹ is NH₂ or NCH₃, in conjunction with any of the above or below embodiments.

30 In another embodiment, the compounds are generally defined by Formula I above, wherein

A² is CH;

A³ is CH;

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R^1 is NR^7R^7 , NR^7R^8 , SR^7 , $C(O)R^7$, $COOR^7$, $C(O)NR^7R^7$, $NR^7C(O)R^7$, $NR^7C(O)NR^7R^7$, $NR^7(COOR^7)$, $C(O)NR^7R^8$, $NR^7C(O)R^8$, $NR^7C(O)NR^7R^8$, $NR^7(COOR^8)$, $S(O)_2R^7$, $S(O)_2NR^7R^7$, $NR^7S(O)_2NR^7R^7$, $NR^7S(O)_2R^7$, $S(O)_2NR^7R^8$, $NR^7S(O)_2NR^7R^8$ or $NR^7S(O)_2R^8$;

- 5 R^2 is a phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl ring system, said ring system substituted independently with 1-3 substituents of R^{10} , R^{11} , R^{15} , $NR^{10}R^{10}$, $NR^{10}R^{11}$, OR^{10} , SR^{10} , OR^{11} , SR^{11} , $C(O)R^{10}$, $C(S)R^{10}$, $C(NCN)R^{10}$, $C(O)R^{11}$, $C(S)R^{11}$, $C(NCN)R^{11}$, $C(O)C(O)R^{10}$, $OC(O)R^{10}$, $COOR^{10}$, $C(O)SR^{10}$, $C(O)C(O)R^{11}$, $OC(O)R^{11}$, $COOR^{11}$, $C(O)SR^{11}$, $C(O)NR^{10}R^{10}$, $C(S)NR^{10}R^{10}$, $C(O)NR^{10}R^{11}$, $C(S)NR^{10}R^{11}$, $OC(O)NR^{10}R^{11}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)R^{11}$, $NR^{10}C(S)R^{10}$, $NR^{10}C(S)R^{11}$, $NR^{10}C(O)NR^{10}R^{10}$, $NR^{10}C(O)NR^{10}R^{11}$, $NR^{10}C(S)NR^{10}R^{10}$, $NR^{10}C(S)NR^{10}R^{11}$, $NR^{10}(COOR^{10})$, $NR^{10}(COOR^{11})$, $NR^{10}C(O)C(O)R^{10}$, $NR^{10}C(O)C(O)R^{11}$, $NR^{10}C(O)C(O)NR^{10}R^{11}$, $S(O)_2R^{10}$, $S(O)_2R^{11}$, $S(O)_2NR^{10}R^{10}$, $S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2R^{10}$ or $NR^{10}S(O)_2R^{11}$, provided that one substituent is $C(O)NR^{10}R^{10}$, $C(S)NR^{10}R^{10}$, $C(O)NR^{10}R^{11}$, $C(S)NR^{10}R^{11}$, $NR^{10}R^{11}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(S)R^{10}$, $NR^{10}C(O)R^{11}$, $NR^{10}C(S)R^{11}$, $NR^{10}C(S)NR^{10}R^{10}$, $NR^{10}C(S)NR^{10}R^{11}$, $S(O)_2NR^{10}R^{10}$, $S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2R^{10}$ or $NR^{10}S(O)_2R^{11}$;

- 25 R^7 is H, C_{1-10} -alkyl or C_{3-10} -cycloalkyl, each of the C_{1-10} -alkyl and C_{3-10} -cycloalkyl optionally comprising 1-2 heteroatoms selected from N, O and S and optionally substituted with 1-3 substituents of R^9 ;

- 30 R^8 is a phenyl, naphthyl, pyridyl, pyrimidinyl, pyrrolidinyl, piperidinyl, piperazinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, tetrahydroquinazolinyl, tetrahydroisoquinazolinyl, morpholinyl, thiophenyl, furyl, dihydrofuryl,

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tetrahydrofuryl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl ring system, said ring system optionally substituted independently with 1-3 substituents of R⁹, oxo, NR⁹R⁹, OR⁹, SR⁹, C(O)R⁹ or a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and optionally substituted independently with 1-3 substituents of R⁹;

alternatively, R⁷ and R⁸ taken together form a 5-6 membered ring selected from pyrrolidine, piperidine, morpholine and piperazine, the ring optionally substituted independently with 1-3 substituents of R⁹;

R⁹ is H, halo, haloalkyl, CN, OH, NO₂, NH₂, acetyl, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl or a ring system of phenyl, naphthyl, pyridyl, pyrimidinyl, pyrrolidinyl, piperidinyl, piperazinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, tetrahydroquinazolinyl, tetrahydroisoquinazolinyl, morpholinyl, thiophenyl, furyl, dihydrofuryl, tetrahydrofuryl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl and benzimidazolyl, wherein each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl and ring system is optionally substituted independently with 1-3 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamine, dimethylamine, ethylamine, diethylamine,

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propylamine, isopropylamine, dipropylamine,
diisopropylamine, benzyl or phenyl;

R^{10} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -
cycloalkyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -
5 alkynyl and C_{3-10} -cycloalkyl optionally comprising 1-4
heteroatoms selected from N, O and S and optionally
substituted with 1-3 substituents of R^{11} , R^{12} or R^{16} , $NR^{11}R^{12}$,
 $NR^{12}R^{12}$, OR^{11} , SR^{11} , OR^{12} , SR^{12} , $C(O)R^{11}$, $OC(O)R^{11}$, $COOR^{11}$,
 $C(O)R^{12}$, $OC(O)R^{12}$, $COOR^{12}$, $C(O)NR^{11}R^{12}$, $NR^{12}C(O)R^{11}$, $C(O)NR^{12}R^{12}$,
10 $NR^{12}C(O)R^{12}$, $NR^{12}C(O)NR^{11}R^{12}$, $NR^{12}C(O)NR^{12}R^{12}$, $NR^{12}(COOR^{11})$,
 $NR^{12}(COOR^{12})$, $OC(O)NR^{11}R^{12}$, $OC(O)NR^{12}R^{12}$, $S(O)_2R^{11}$, $S(O)_2R^{12}$,
 $S(O)_2NR^{11}R^{12}$, $S(O)_2NR^{12}R^{12}$, $NR^{12}S(O)_2NR^{11}R^{12}$, $NR^{12}S(O)_2NR^{12}R^{12}$,
 $NR^{12}S(O)_2R^{11}$, $NR^{12}S(O)_2R^{12}$, $NR^{12}S(O)_2R^{11}$ or $NR^{12}S(O)_2R^{12}$;

R^{11} is a phenyl, naphthyl, pyridyl, pyrimidinyl,
15 quinolinyl, isoquinolinyl, tetrahydroquinolinyl,
tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl,
tetrahydroquinazolinyl, tetrahydroisoquinazolinyl,
thiophenyl, furyl, pyrrolyl, imidazolyl, thiazolyl,
oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl,
20 indolinyl, benzofuranyl, dihydrobenzofuranyl,
benzothiophenyl or benzimidazolyl ring system, said ring
system optionally substituted independently with 1-3
substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

alternatively, R^{10} and R^{11} taken together form a
25 partially or fully saturated or unsaturated 5-6 membered
ring of carbon atoms optionally including 1-3 heteroatoms
selected from O, N, or S, said ring optionally substituted
independently with 1-3 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -
30 cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -
dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which
is optionally substituted independently with 1-3
substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

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R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} , SR^{14} , OR^{15} , SR^{15} , $C(O)R^{14}$, $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$, $C(O)NR^{15}R^{15}$, $NR^{14}C(O)R^{14}$, $NR^{15}C(O)R^{14}$, $NR^{14}C(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(O)NR^{14}R^{15}$, $NR^{15}C(O)NR^{15}R^{15}$, $NR^{15}(COOR^{14})$, $NR^{15}(COOR^{15})$,
 5 $OC(O)NR^{14}R^{15}$, $OC(O)NR^{15}R^{15}$, $S(O)_2R^{14}$, $S(O)_2R^{15}$, $S(O)_2NR^{14}R^{15}$, $S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2NR^{14}R^{15}$, $NR^{15}S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2R^{14}$ or $NR^{15}S(O)_2R^{15}$;

R^{14} is phenyl, naphthyl, pyridyl, pyrimidinyl, pyrrolidinyl, piperidinyl, piperazinyl, quinolinyl,
 10 isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, tetrahydroquinazolinyl, tetrahydroisoquinazolinyl, morpholinyl, thiophenyl, furyl, dihydrofuryl, tetrahydrofuryl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl,
 15 isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl, benzofuranyl, dihydrobenzofuranyl, benzoxazinyl, benzodioxazinyl, benzothiophenyl and benzimidazolyl, each of which is optionally substituted independently with 1-5 substituents of R^{15} or R^{16} ;

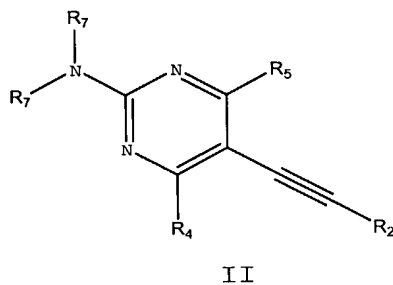
20 R^{15} is H or C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkoxyl, each of which is optionally substituted independently with 1-5 substituents of R^{16} ; and

25 R^{16} is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a
 30 partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally

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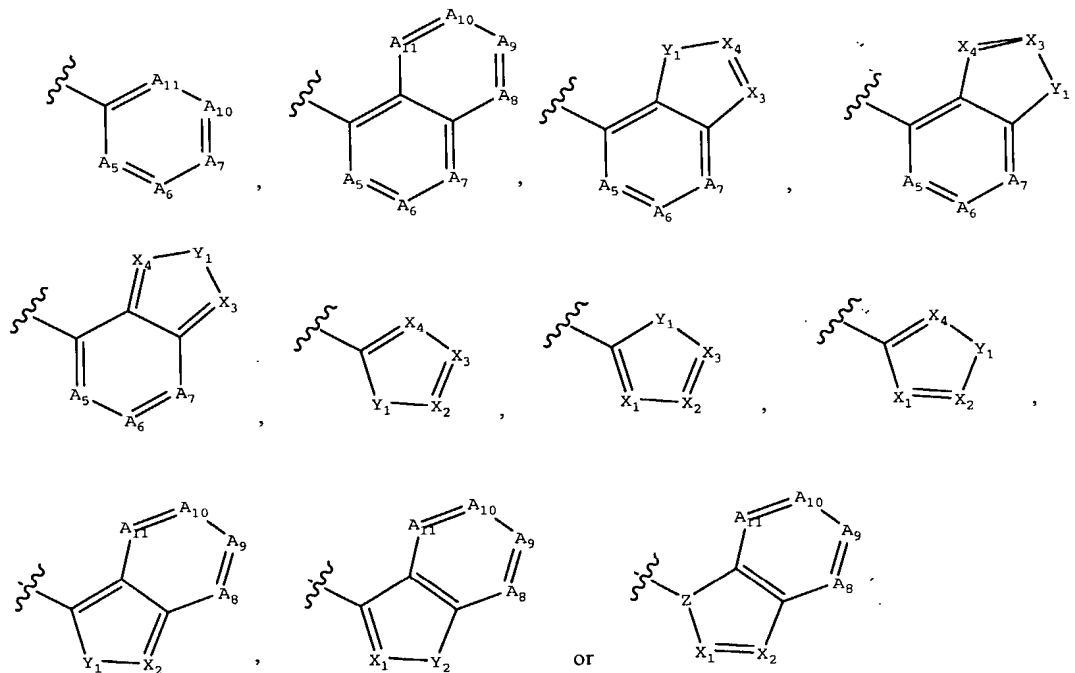
substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

In yet another embodiment, the compounds are generally defined by Formula II



10 wherein

R² is



wherein

one of A⁶ and A⁷ is CR^{3a} and the other of A⁶ and A⁷

15

is CR^{3b} or N;

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each of A^5 , A^8 , A^9 , A^{10} and A^{11} is, independently,
 CR^{3b} or N;

X^2 is CR^{3a} ;

each of X^1 , X^3 and X^4 is, independently, CR^{3b} or N;

5 Y^1 is $CR^{3b}R^{3c}$, NR^{3c} , O or S;

Y^2 is $CR^{3a}R^{3b}$ or NR^{3a} ; and

Z is CH or N;

R^{3a} is $OC(O)R^{10}$, $COOR^{10}$, $OC(O)R^{11}$, $COOR^{11}$, $C(O)SR^{10}$,
 $C(O)SR^{11}$, $C(O)NR^{10}R^{10}$, $C(S)NR^{10}R^{10}$, $C(O)NR^{10}R^{11}$, $C(S)NR^{10}R^{11}$,
 10 $NR^{10}R^{11}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(S)R^{10}$, $NR^{10}C(O)R^{11}$, $NR^{10}C(S)R^{11}$,
 $NR^{10}C(S)NR^{10}R^{10}$, $NR^{10}C(S)NR^{10}R^{11}$, $OC(O)NR^{10}R^{11}$, $S(O)_2R^{11}$,
 $S(O)_2NR^{10}R^{10}$, $S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2R^{10}$ or
 $NR^{10}S(O)_2R^{11}$;

R^{3b} is H, halo, haloalkyl, CN, NO_2 , NH_2 , C_{1-10} -
 15 alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl;
 and

R^{3c} is H, CN or C_{1-10} -alkyl;

R^4 is H, halo, haloalkyl, NO_2 , CN, OH, O- C_{1-10} -alkyl,
 NH_2 , C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -
 20 cycloalkyl;

R^5 is H, halo, haloalkyl, NO_2 , CN, OH, NH_2 , O- C_{1-10} -
 alkyl, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -
 cycloalkyl;

Each R^7 , independently, is H, R^8 , C_{1-10} -alkyl, C_{2-10} -
 25 alkenyl or C_{2-10} -alkynyl, each of which is optionally
 substituted with 1-3 substituents of NR^8R^9 , NR^9R^9 , OR^8 , SR^8 ,
 OR^9 , SR^9 , $C(O)R^8$, $C(O)R^9$, $C(O)NR^8R^9$, $C(O)NR^9R^9$, $S(O)_2R^8$,
 $S(O)_2NR^8R^9$, $S(O)_2R^9$, $S(O)_2NR^9R^9$, R^8 or R^9 ;

alternatively, NR^7R^7 form a 5-6 membered heterocyclic
 30 ring selected from pyrrolidine, piperidine, morpholine and
 piperazine, the ring optionally substituted independently
 with 1-3 substituents of R^9 ;

R^8 is a ring system selected from phenyl, naphthyl,
 pyridyl, piperazinyl, triazinyl, thiophenyl, furyl,

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pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuran-
pyrrolidinyl, oxazolinyl, isoxazolinyl, thiazolinyl,
5 pyrazolinyl, morpholinyl, piperidinyl, pyranyl, dioxozinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, said ring system optionally substituted independently with 1-3 substituents of R^9 , oxo, NR^9R^9 , OR^9 , SR^9 , $C(O)R^9$, phenyl, pyridyl, piperidyl, piperazinyl,
10 morpholinyl or pyrrolidinyl;

R^9 is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , acetyl, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl, C_{1-10} -thioalkoxyl or a ring system selected from
15 phenyl, naphthyl, pyridyl, piperazinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuran-
20 pyrrolidinyl, oxazolinyl, isoxazolinyl, thiazolinyl, pyrazolinyl, morpholinyl, piperidinyl, piperazinyl, pyranyl, dioxozinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl, C_{1-10} -thioalkoxyl and ring system optionally
25 substituted independently with 1-3 substituents of halo, haloalkyl, CN, NO_2 , NH_2 , OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino,
30 ethylamino, diethylamino, propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;

R^{10} is H, halo, haloalkyl, CN, NO_2 , C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl or C_{4-10} -cycloalkenyl,

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each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl and C₄₋₁₀-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents of R¹¹, R¹² or R¹⁶,
 5 NR¹¹R¹², NR¹²R¹², OR¹¹, SR¹¹, OR¹², SR¹², C(O)R¹¹, OC(O)R¹¹, COOR¹¹, C(O)R¹², OC(O)R¹², COOR¹², C(O)NR¹¹R¹², NR¹²C(O)R¹¹, C(O)NR¹²R¹², NR¹²C(O)R¹², NR¹²C(O)NR¹¹R¹², NR¹²C(O)NR¹²R¹², NR¹²(COOR¹¹), NR¹²(COOR¹²), OC(O)NR¹¹R¹², OC(O)NR¹²R¹², S(O)₂R¹¹, S(O)₂R¹², S(O)₂NR¹¹R¹², S(O)₂NR¹²R¹², NR¹²S(O)₂NR¹¹R¹², NR¹²S(O)₂NR¹²R¹²,
 10 NR¹²S(O)₂R¹¹, NR¹²S(O)₂R¹², NR¹²S(O)₂R¹¹ or NR¹²S(O)₂R¹²;

R¹¹ is a phenyl, naphthyl, 5,6,7,8-tetrahydronaphthyl, dihydro-indenyl, pyridyl, pyrimidinyl, triazinyl, quinolinyl, tetrahydroquinolinyl, oxo-tetrahydroquinolinyl, isoquinolinyl, oxo-tetrahydroisoquinolinyl,
 15 tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, tetrahydrofuranlyl, pyrrolyl, pyrazolyl, thieno-pyrazolyl, tetrahydropentapyrazolyl, imidazolyl, triazolyl, tetrazolyl, thiazolyl, thiadiazolyl, benzothiazolyl, oxazolyl, oxadiazolyl, benzoxazolyl,
 20 benzoxadiazolyl, isoxazolyl, isothiazolyl, indolyl, azaindolyl, 2,3-dihydroindolyl, isoindolyl, indazolyl, benzofuranlyl, benzothiophenyl, benzimidazolyl, imidazo-pyridinyl, purinyl, benzotriazolyl, oxazolinyl, isoxazolinyl, thiazolinyl, pyrrolidinyl, pyrazolinyl,
 25 morpholinyl, piperidinyl, piperazinyl, pyranlyl, dioxozinyl, 2,3-dihydro-1,4-benzoxazinyl, 1,3-benzodioxolyl, cyclopropyl, cyclobutyl, azetidyl, cyclopentyl, cyclohexyl or cycloheptyl ring system, said ring system optionally substituted independently with 1-3 substituents of R¹², R¹³,
 30 R¹⁴ or R¹⁶;

alternatively, R¹⁰ and R¹¹ taken together form a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally

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substituted independently with 1-3 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which
5 is optionally substituted independently with 1-3 substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} , SR^{14} , OR^{15} , SR^{15} , $C(O)R^{14}$, $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$,
10 $C(O)NR^{15}R^{15}$, $NR^{14}C(O)R^{14}$, $NR^{15}C(O)R^{14}$, $NR^{14}C(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(O)NR^{14}R^{15}$, $NR^{15}C(O)NR^{15}R^{15}$, $NR^{15}(COOR^{14})$, $NR^{15}(COOR^{15})$, $OC(O)NR^{14}R^{15}$, $OC(O)NR^{15}R^{15}$, $S(O)_2R^{14}$, $S(O)_2R^{15}$, $S(O)_2NR^{14}R^{15}$, $S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2NR^{14}R^{15}$, $NR^{15}S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2R^{14}$ or $NR^{15}S(O)_2R^{15}$;

R^{14} is phenyl, pyridyl, pyrimidinyl, thiophenyl, furyl, tetrahydrofuryl, pyrrolyl, pyrazolyl, thieno-pyrazolyl, imidazolyl, triazolyl, thiazolyl, thiadiazolyl, benzothiazolyl, oxazolyl, oxadiazolyl, benzoxazolyl, benzoxadiazolyl, isoxazolyl, isothiazolyl, indolyl,
20 azaindolyl, isoindolyl, indazolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, pyrrolidinyl, pyrazolinyl, morpholinyl, piperidinyl, piperazinyl, 2,3-dihydro-1,4-benzoxazinyl, 1,3-benzodioxolyl, cyclopropyl, cyclobutyl, azetidiny, cyclopentyl and cyclohexyl, each of which is
25 optionally substituted independently with 1-3 substituents of R^{15} or R^{16} ;

R^{15} is H or C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkoxyl, each of
30 which is optionally substituted independently with 1-3 substituents of R^{16} ; and

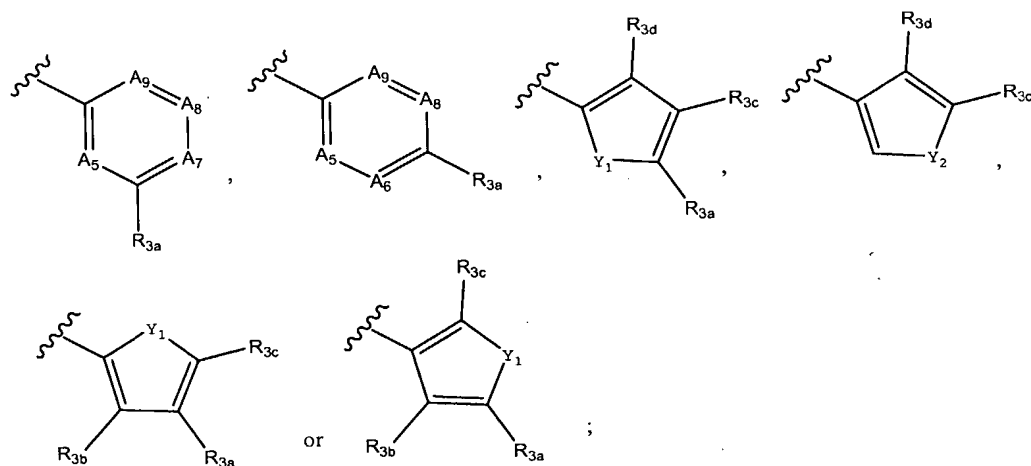
R^{16} is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino,

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dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

In another embodiment, the compounds are defined by Formula II above, wherein:

15 R² is



wherein

each of A⁵, A⁶, and A⁷ is, independently, CR^{3b} or

20 N;

A⁸ is CR^{3c} or N; and

A⁹ is CR^{3d} or N;

Y¹ is O or S;

Y² is NR^{3a};

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5 R^{3a} is $COOR^{10}$, $COOR^{11}$, $C(O)SR^{10}$, $C(O)SR^{11}$,
 $C(O)NR^{10}R^{10}$, $C(S)NR^{10}R^{10}$, $C(O)NR^{10}R^{11}$, $C(S)NR^{10}R^{11}$, $NR^{10}R^{11}$,
 $NR^{10}C(O)R^{10}$, $NR^{10}C(S)R^{10}$, $NR^{10}C(O)R^{11}$, $NR^{10}C(S)R^{11}$,
 $NR^{10}C(S)NR^{10}R^{10}$, $NR^{10}C(S)NR^{10}R^{11}$, $S(O)_2NR^{10}R^{10}$, $S(O)_2NR^{10}R^{11}$,
 $NR^{10}S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2R^{10}$ or $NR^{10}S(O)_2R^{11}$;

R^{3b} is H, halo, haloalkyl, CN, NO_2 , NH_2 , C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl;
 R^{3c} is H, halo, haloalkyl, CN, NO_2 , NH_2 , C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl;

10 R^{3c} is H, halo, haloalkyl, CN, NO_2 , NH_2 , C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl;

R^{3d} is H, halo, haloalkyl, CN, NO_2 , NH_2 , C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl;
 and

15 alternatively, R^{3c} and R^{3d} taken together with the atoms to which they are attached form a phenyl or tetrahydrofuran ring system, optionally substituted with 1-3 substituents of halo, haloalkyl, CN, NO_2 , NH_2 , C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl;

20 R^4 is H, C_{1-10} -alkyl or O- C_{1-10} -alkyl;

R^5 is H, C_{1-10} -alkyl or O- C_{1-10} -alkyl;

R^7 is H or C_{1-10} -alkyl;

R^8 is H or C_{1-10} -alkyl;

25 R^{10} is H, halo, haloalkyl, CN, NO_2 , C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl or C_{4-10} -cycloalkenyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl and C_{4-10} -cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally
 30 substituted with one or more substituents of R^{11} , R^{12} or R^{16} , $NR^{11}R^{12}$, $NR^{12}R^{12}$, OR^{11} , SR^{11} , OR^{12} , SR^{12} , $C(O)R^{11}$, $OC(O)R^{11}$, $COOR^{11}$, $C(O)R^{12}$, $OC(O)R^{12}$, $COOR^{12}$, $C(O)NR^{11}R^{12}$, $NR^{12}C(O)R^{11}$, $C(O)NR^{12}R^{12}$, $NR^{12}C(O)R^{12}$, $NR^{12}C(O)NR^{11}R^{12}$, $NR^{12}C(O)NR^{12}R^{12}$, $NR^{12}(COOR^{11})$, $NR^{12}(COOR^{12})$, $OC(O)NR^{11}R^{12}$, $OC(O)NR^{12}R^{12}$, $S(O)_2R^{11}$, $S(O)_2R^{12}$,

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$S(O)_2NR^{11}R^{12}$, $S(O)_2NR^{12}R^{12}$, $NR^{12}S(O)_2NR^{11}R^{12}$, $NR^{12}S(O)_2NR^{12}R^{12}$,
 $NR^{12}S(O)_2R^{11}$, $NR^{12}S(O)_2R^{12}$, $NR^{12}S(O)_2R^{11}$ or $NR^{12}S(O)_2R^{12}$;

R^{11} is a phenyl, naphthyl, 5,6,7,8-tetrahydronaphthyl,
dihydro-indenyl, pyridyl, pyrimidinyl, triazinyl,
5 quinolinyl, tetrahydroquinolinyl, oxo-tetrahydroquinolinyl,
isoquinolinyl, oxo-tetrahydroisoquinolinyl,
tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl,
thiophenyl, furyl, tetrahydrofuranlyl, pyrrolyl, pyrazolyl,
thieno-pyrazolyl, tetrahydropentapyrazolyl, imidazolyl,
10 triazolyl, tetrazolyl, thiazolyl, thiadiazolyl,
benzothiazolyl, oxazolyl, oxadiazolyl, benzoxazolyl,
benzoxadiazolyl, isoxazolyl, isothiazolyl, indolyl,
azaindolyl, 2,3-dihydroindolyl, isoindolyl, indazolyl,
benzofuranlyl, benzothiophenyl, benzimidazolyl, imidazo-
15 pyridinyl, purinyl, benzotriazolyl, oxazolinyl,
isoxazolinyl, thiazolinyl, pyrrolidinyl, pyrazolinyl,
morpholinyl, piperidinyl, piperazinyl, pyranlyl, dioxozinyl,
2,3-dihydro-1,4-benzoxazinyl, 1,3-benzodioxolyl,
cyclopropyl, cyclobutyl, azetidiny, cyclopentyl, cyclohexyl
20 or cycloheptyl ring system, said ring system optionally
substituted independently with 1-3 substituents of R^{12} , R^{13} ,
 R^{14} or R^{16} ;

alternatively, R^{10} and R^{11} taken together form a
partially or fully saturated or unsaturated 5-6 membered
25 ring of carbon atoms optionally including 1-3 heteroatoms
selected from O, N, or S, and the ring optionally
substituted independently with 1-3 substituents of R^{12} , R^{13} ,
 R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -
30 cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -
dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which
is optionally substituted independently with 1-3
substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

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R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} , SR^{14} , OR^{15} , SR^{15} , $C(O)R^{14}$, $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$, $C(O)NR^{15}R^{15}$, $NR^{14}C(O)R^{14}$, $NR^{15}C(O)R^{14}$, $NR^{14}C(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(O)NR^{14}R^{15}$, $NR^{15}C(O)NR^{15}R^{15}$, $NR^{15}(COOR^{14})$, $NR^{15}(COOR^{15})$,
5 $OC(O)NR^{14}R^{15}$, $OC(O)NR^{15}R^{15}$, $S(O)_2R^{14}$, $S(O)_2R^{15}$, $S(O)_2NR^{14}R^{15}$, $S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2NR^{14}R^{15}$, $NR^{15}S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2R^{14}$ or $NR^{15}S(O)_2R^{15}$;

R^{14} is phenyl, pyridyl, pyrimidinyl, thiophenyl, furyl, tetrahydrofuryl, pyrrolyl, pyrazolyl, thieno-pyrazolyl,
10 imidazolyl, triazolyl, thiazolyl, thiadiazolyl, benzothiazolyl, oxazolyl, oxadiazolyl, benzoxazolyl, benzoxadiazolyl, isoxazolyl, isothiazolyl, indolyl, azaindolyl, isoindolyl, indazolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, pyrrolidinyl, pyrazolinyl,
15 morpholinyl, piperidinyl, piperazinyl, 2,3-dihydro-1,4-benzoxazinyl, 1,3-benzodioxolyl, cyclopropyl, cyclobutyl, azetidiny, cyclopentyl and cyclohexyl, each of which is optionally substituted independently with 1-3 substituents of R^{15} or R^{16} ;

R^{15} is H or C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkoxyl, each of which is optionally substituted independently with 1-5 substituents of R^{16} ; and

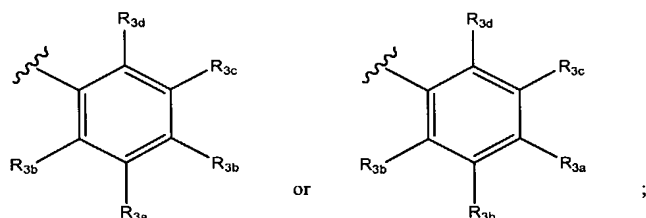
R^{16} is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a
25 partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally
30

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substituted independently with 1-5 substituents of halo,
haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl,
ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl,
isobutyl, tert-butyl, methylamino, dimethylamino,
5 ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

In another embodiment, the compounds are generally
defined by Formula II, wherein:

R² is



10 wherein

R^{3a} is COOR¹⁰, COOR¹¹, C(O)SR¹⁰, C(O)SR¹¹, C(O)NR¹⁰R¹⁰,
C(O)NR¹⁰R¹¹, NR¹⁰R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(O)R¹¹, S(O)₂NR¹⁰R¹⁰,
S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂R¹⁰ or NR¹⁰S(O)₂R¹¹;

each of R^{3b}, R^{3c} and R^{3d}, independently, is H, F, Cl,
15 Br, I, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, CN, NO₂, NH₂, methyl, ethyl,
propyl, isopropyl, n-butyl, sec-butyl, tert-butyl,
acetylenyl, cyclopropyl, cyclobutyl, cyclopentyl,
cyclohexyl, OH, methoxyl, ethoxyl, propoxyl, SH, thiomethyl
or thioethyl;

20 each of R⁴ and R⁵, independently, is H, F, Cl, Br, I,
CF₃, CF₂CF₃, OCF₃, CN, methyl, ethyl, propyl, isopropyl, n-
butyl, sec-butyl, tert-butyl, OH, methoxyl, ethoxyl,
propoxyl;

each R⁷, independently, is H, C(O)R⁸, COOR⁸, C(O)R⁹,
25 COOR⁹, C(O)NR⁸R⁹, C(O)NR⁹R⁹, S(O)₂R⁸, S(O)₂NR⁸R⁹, S(O)₂R⁹,
S(O)₂NR⁹R⁹, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-
cycloalkyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-
alkynyl and C₃₋₁₀-cycloalkyl optionally comprising 1-4
heteroatoms selected from N, O and S and optionally
30 substituted with one or more substituents of NR⁸R⁹, NR⁹R⁹,

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OR⁸, SR⁸, OR⁹, SR⁹, C(O)R⁸, C(O)R⁹, C(O)NR⁸R⁹, C(O)NR⁹R⁹,
 NR⁹C(O)R⁸, NR⁹C(O)R⁹, NR⁹C(O)NR⁸R⁹, NR⁹C(O)NR⁹R⁹, NR⁹(COOR⁸),
 NR⁹(COOR⁹), S(O)₂R⁸, S(O)₂NR⁸R⁹, S(O)₂R⁹, S(O)₂NR⁹R⁹,
 NR⁹S(O)₂NR⁸R⁹, NR⁹S(O)₂NR⁹R⁹, NR⁹S(O)₂R⁸, NR⁹S(O)₂R⁹, R⁸ or R⁹;

- 5 R⁸ is a phenyl, naphthyl, pyridyl, piperazinyl,
 triazinyl, quinolinyl, isoquinolinyl, quinazolinyl,
 isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl,
 triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl,
 indolyl, isoindolyl, benzofuranyl, benzothiophenyl,
 10 benzimidazolyl, tetrahydrofuranyl, pyrrolidinyl, oxazolyl,
 isoxazolyl, thiazolyl, pyrazolyl, morpholyl,
 piperidinyl, piperazinyl, pyranyl, dioxozinyl, cyclopropyl,
 cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl ring
 system, said ring system optionally substituted
 15 independently with 1-3 substituents of R⁹, oxo, NR⁹R⁹, OR⁹;
 SR⁹, C(O)R⁹, phenyl, pyridyl, piperidinyl, piperazinyl or
 morpholyl;
- R⁹ is H, halo, haloalkyl, CN, OH, NO₂, NH₂, acetyl, C₁-
 10-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₁₋₁₀-
 20 alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-
 thioalkoxyl or a ring system selected from phenyl, naphthyl,
 pyridyl, piperazinyl, triazinyl, quinolinyl, isoquinolinyl,
 quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl,
 imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl,
 25 isothiazolyl, indolyl, isoindolyl, benzofuranyl,
 benzothiophenyl, benzimidazolyl, tetrahydrofuranyl,
 pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl,
 pyrazolyl, morpholyl, piperidinyl, piperazinyl, pyranyl
 and dioxozinyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-
 30 alkynyl, C₃₋₁₀-cycloalkyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-
 dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl and ring system
 optionally substituted independently with 1-3 substituents
 of halo, haloalkyl, CN, NO₂, NH₂, OH, oxo, methyl, methoxyl,
 ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl,

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butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;

R^{10} is H, methyl, ethyl, propyl, isopropyl, n-butyl, 5 sec-butyl, tert-butyl, acetylenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, OH, methoxyl, ethoxyl, propoxyl, SH, thiomethyl or thioethyl; each of which is optionally substituted with one or more substituents of R^{11} , R^{12} or R^{16} ;

R^{11} is a phenyl, naphthyl, 5,6,7,8-tetrahydronaphthyl, 10 dihydro-indenyl, pyridyl, pyrimidinyl, triazinyl, quinolinyl, tetrahydroquinolinyl, oxo-tetrahydroquinolinyl, isoquinolinyl, oxo-tetrahydroisoquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, tetrahydrofuranlyl, pyrrolyl, pyrazolyl, 15 thieno-pyrazolyl, tetrahydropentapyrazolyl, imidazolyl, triazolyl, tetrazolyl, thiazolyl, thiadiazolyl, benzothiazolyl, oxazolyl, oxadiazolyl, benzoxazolyl, benzoxadiazolyl, isoxazolyl, isothiazolyl, indolyl, azaindolyl, 2,3-dihydroindolyl, isoindolyl, indazolyl, 20 benzofuranlyl, benzothiophenyl, benzimidazolyl, imidazo-pyridinyl, purinyl, benzotriazolyl, oxazolinyl, isoxazolinyl, thiazolinyl, pyrrolidinyl, pyrazolinyl, morpholinyl, piperidinyl, piperazinyl, pyranlyl, dioxozinyl, 2,3-dihydro-1,4-benzoxazinyl, 1,3-benzodioxolyl; 25 cyclopropyl, cyclobutyl, azetidiny, cyclopentyl, cyclohexyl or cycloheptyl ring system, said ring system optionally substituted independently with 1-3 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

alternatively, R^{10} and R^{11} taken together form a 30 partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-3 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

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R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which is optionally substituted independently with 1-3

5 substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} ; SR^{14} , OR^{15} ; SR^{15} , $C(O)R^{14}$, $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$, $C(O)NR^{15}R^{15}$, $NR^{14}C(O)R^{14}$, $NR^{15}C(O)R^{14}$, $NR^{14}C(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(O)NR^{14}R^{15}$, $NR^{15}C(O)NR^{15}R^{15}$, $NR^{15}(COOR^{14})$, $NR^{15}(COOR^{15})$,
10 $OC(O)NR^{14}R^{15}$, $OC(O)NR^{15}R^{15}$, $S(O)_2R^{14}$, $S(O)_2R^{15}$, $S(O)_2NR^{14}R^{15}$, $S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2NR^{14}R^{15}$, $NR^{15}S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2R^{14}$ or $NR^{15}S(O)_2R^{15}$;

R^{14} is phenyl, pyridyl, pyrimidinyl, thiophenyl, furyl, tetrahydrofuryl, pyrrolyl, pyrazolyl, thieno-pyrazolyl,
15 imidazolyl, triazolyl, thiazolyl, thiadiazolyl, benzothiazolyl, oxazolyl, oxadiazolyl, benzoxazolyl, benzoxadiazolyl, isoxazolyl, isothiazolyl, indolyl, azaindolyl, isoindolyl, indazolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, pyrrolidinyl, pyrazolinyl,
20 morpholinyl, piperidinyl, piperazinyl, 2,3-dihydro-1,4-benzoxazinyl, 1,3-benzodioxolyl, cyclopropyl, cyclobutyl, azetidyl, cyclopentyl and cyclohexyl, each of which is optionally substituted independently with 1-3 substituents of R^{15} or R^{16} ;

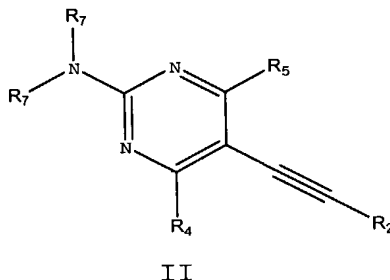
25 R^{15} is H or C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkoxyl, each of which is optionally substituted independently with 1-3 substituents of R^{16} ; and

30 R^{16} is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a

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partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

In another embodiment, the compounds are generally defined by Formula II



wherein

R² is a phenyl, naphthyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl or isoindolyl ring system, said ring system substituted independently with 0-3 substituents of R¹⁰, R¹¹ or R¹⁵ and one substituent, meta or para to the point of attachment of the alkyne on the R² ring, is NR¹⁰C(O)NR¹⁰R¹⁰, NR¹⁰C(O)NR¹⁰R¹¹, NR¹⁰(COOR¹⁰) or NR¹⁰(COOR¹¹);

R⁷ is H, C₁₋₁₀-alkyl or C₃₋₁₀-cycloalkyl, each of the C₁₋₁₀-alkyl and C₃₋₁₀-cycloalkyl optionally comprising 1-2 heteroatoms selected from N, O and S and optionally substituted with 1-3 substituents of R⁹;

R⁸ is a phenyl, naphthyl, pyridyl, pyrimidinyl, pyrrolidinyl, piperidinyl, piperazinyl, quinolinyl,

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- isoquinolinyl, tetrahydroquinolinyl,
tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl,
tetrahydroquinazolinyl, tetrahydroisoquinazolinyl,
morpholinyl, thiophenyl, furyl, dihydrofuryl,
5 tetrahydrofuryl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl,
isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl,
benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or
benzimidazolyl ring system, said ring system optionally
substituted independently with 1-3 substituents of R^9 , oxo,
10 NR^9R^9 , OR^9 ; SR^9 , $C(O)R^9$ or a partially or fully saturated or
unsaturated 5-6 membered ring of carbon atoms optionally
including 1-3 heteroatoms selected from O, N, or S, and
optionally substituted independently with 1-3 substituents
of R^9 ;
15 alternatively, R^7 and R^8 taken together form a 5-6
membered ring selected from pyrrolidine, piperidine,
morpholine and piperazine, the ring optionally substituted
independently with 1-3 substituents of R^9 ;
 R^9 is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , acetyl, C_{1-}
20 $_{10}$ -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{1-10} -
alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl, C_{1-10} -
thioalkoxyl or a ring system of phenyl, naphthyl, pyridyl,
pyrimidinyl, pyrrolidinyl, piperidinyl, piperazinyl,
quinolinyl, isoquinolinyl, tetrahydroquinolinyl,
25 tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl,
tetrahydroquinazolinyl, tetrahydroisoquinazolinyl,
morpholinyl, thiophenyl, furyl, dihydrofuryl,
tetrahydrofuryl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl,
isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl,
30 benzofuranyl, dihydrobenzofuranyl, benzothiophenyl and
benzimidazolyl, wherein each of the C_{1-10} -alkyl, C_{2-10} -alkenyl,
 C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -
alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl, C_{1-10} -
thioalkoxyl and ring system is optionally substituted

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independently with 1-3 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamine, dimethylamine, ethylamine, diethylamine, 5 propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;

R¹⁰ is H, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-cycloalkyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl and C₃₋₁₀-cycloalkyl optionally comprising 1-4 10 heteroatoms selected from N, O and S and optionally substituted with 1-3 substituents of R¹¹, R¹² or R¹⁶, NR¹¹R¹², NR¹²R¹², OR¹¹, SR¹¹, OR¹², SR¹², C(O)R¹¹, OC(O)R¹¹, COOR¹¹, C(O)R¹², OC(O)R¹², COOR¹², C(O)NR¹¹R¹², NR¹²C(O)R¹¹, C(O)NR¹²R¹², NR¹²C(O)R¹², NR¹²C(O)NR¹¹R¹², NR¹²C(O)NR¹²R¹², NR¹²(COOR¹¹), 15 NR¹²(COOR¹²), OC(O)NR¹¹R¹², OC(O)NR¹²R¹², S(O)₂R¹¹, S(O)₂R¹², S(O)₂NR¹¹R¹², S(O)₂NR¹²R¹², NR¹²S(O)₂NR¹¹R¹², NR¹²S(O)₂NR¹²R¹², NR¹²S(O)₂R¹¹, NR¹²S(O)₂R¹², NR¹²S(O)₂R¹¹ or NR¹²S(O)₂R¹²;

R¹¹ is a phenyl, naphthyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, 20 tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, tetrahydroquinazolinyl, tetrahydroisoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl, benzofuranyl, dihydrobenzofuranyl, 25 benzothiophenyl or benzimidazolyl ring system, said ring system optionally substituted independently with 1-3 substituents of R¹², R¹³, R¹⁴ or R¹⁶;

alternatively, R¹⁰ and R¹¹ taken together form a partially or fully saturated or unsaturated 5-6 membered 30 ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, said ring optionally substituted independently with 1-3 substituents of R¹², R¹³, R¹⁴ or R¹⁶;

R¹² is H, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-

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dialkylamino-, C₁₋₁₀-alkoxyl or C₁₋₁₀-thioalkyl, each of which is optionally substituted independently with 1-3 substituents of R¹³, R¹⁴, R¹⁵ or R¹⁶;

R¹³ is NR¹⁴R¹⁵, NR¹⁵R¹⁵, OR¹⁴; SR¹⁴, OR¹⁵; SR¹⁵, C(O)R¹⁴,
 5 OC(O)R¹⁴, COOR¹⁴, C(O)R¹⁵, OC(O)R¹⁵, COOR¹⁵, C(O)NR¹⁴R¹⁵,
 C(O)NR¹⁵R¹⁵, NR¹⁴C(O)R¹⁴, NR¹⁵C(O)R¹⁴, NR¹⁴C(O)R¹⁵, NR¹⁵C(O)R¹⁵,
 NR¹⁵C(O)NR¹⁴R¹⁵, NR¹⁵C(O)NR¹⁵R¹⁵, NR¹⁵(COOR¹⁴), NR¹⁵(COOR¹⁵),
 OC(O)NR¹⁴R¹⁵, OC(O)NR¹⁵R¹⁵, S(O)₂R¹⁴, S(O)₂R¹⁵, S(O)₂NR¹⁴R¹⁵,
 S(O)₂NR¹⁵R¹⁵, NR¹⁴S(O)₂NR¹⁴R¹⁵, NR¹⁵S(O)₂NR¹⁵R¹⁵, NR¹⁴S(O)₂R¹⁴ or
 10 NR¹⁵S(O)₂R¹⁵;

R¹⁴ is phenyl, naphthyl, pyridyl, pyrimidinyl,
 pyrrolidinyl, piperidinyl, piperazinyl, quinolinyl,
 isoquinolinyl, tetrahydroquinolinyl,
 tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl,
 15 tetrahydroquinazolinyl, tetrahydroisoquinazolinyl,
 morpholinyl, thiophenyl, furyl, dihydrofuryl,
 tetrahydrofuryl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl,
 isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl,
 benzofuranyl, dihydrobenzofuranyl, benzoxazinyl,
 20 benzodioxazinyl, benzothiophenyl and benzimidazolyl, each of
 which is optionally substituted independently with 1-5
 substituents of R¹⁵ or R¹⁶;

R¹⁵ is H or C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-
 cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-
 25 dialkylamino-, C₁₋₁₀-alkoxyl or C₁₋₁₀-thioalkoxyl, each of
 which is optionally substituted independently with 1-5
 substituents of R¹⁶; and

R¹⁶ is H, halo, haloalkyl, CN, OH, NO₂, NH₂, OH, methyl,
 methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl,
 30 cyclopropyl, butyl, isobutyl, tert-butyl, methylamino,
 dimethylamino, ethylamino, diethylamino, isopropylamino,
 oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a
 partially or fully saturated or unsaturated 5-8 membered
 monocyclic or 6-12 membered bicyclic ring system, said ring

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system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

In another embodiment, the compounds are generally defined by Formula I wherein

A¹ and A⁴, independently, are N;

A² is CR⁴;

A³ is CR⁵;

R¹ is SR⁷, OR⁸, SR⁸, C(O)R⁷, OC(O)R⁷, COOR⁷, C(O)R⁸, OC(O)R⁸, COOR⁸, C(O)NR⁷R⁷, C(S)NR⁷R⁷, NR⁷C(O)R⁷, NR⁷C(S)R⁷, NR⁷C(O)NR⁷R⁷, NR⁷C(S)NR⁷R⁷, NR⁷(COOR⁷), OC(O)NR⁷R⁷, C(O)NR⁷R⁸, C(S)NR⁷R⁸, NR⁷C(O)R⁸, NR⁷C(S)R⁸, NR⁷C(O)NR⁷R⁸, NR⁷C(S)NR⁷R⁸, NR⁷(COOR⁸), OC(O)NR⁷R⁸, S(O)₂R⁷, S(O)₂NR⁷R⁷, NR⁷S(O)₂NR⁷R⁷, NR⁷S(O)₂R⁸, S(O)₂R⁸, S(O)₂NR⁷R⁸, NR⁷S(O)₂NR⁷R⁸ or NR⁷S(O)₂R⁸;

R² is a phenyl, naphthyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, phthalazinyl, aza-phthalazinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, thiadiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl ring system, said ring system substituted independently with 1-5 substituents of R¹⁰, R¹¹, R¹⁵, NR¹⁰R¹⁰, NR¹⁰R¹¹, OR¹⁰, SR¹⁰, OR¹¹, SR¹¹, C(O)R¹⁰, C(S)R¹⁰, C(NCN)R¹⁰, C(O)R¹¹, C(S)R¹¹, C(NCN)R¹¹, C(O)C(O)R¹⁰, OC(O)R¹⁰, COOR¹⁰, C(O)SR¹⁰, C(O)C(O)R¹¹, OC(O)R¹¹, COOR¹¹, C(O)SR¹¹, C(O)NR¹⁰R¹⁰, C(S)NR¹⁰R¹⁰, C(O)NR¹⁰R¹¹, C(S)NR¹⁰R¹¹, OC(O)NR¹⁰R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(O)R¹¹, NR¹⁰C(S)R¹⁰, NR¹⁰C(S)R¹¹, NR¹⁰C(O)NR¹⁰R¹⁰, NR¹⁰C(O)NR¹⁰R¹¹, NR¹⁰C(S)NR¹⁰R¹⁰, NR¹⁰C(S)NR¹⁰R¹¹, NR¹⁰(COOR¹⁰),

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- $\text{NR}^{10}(\text{COOR}^{11})$, $\text{NR}^{10}\text{C}(\text{O})\text{C}(\text{O})\text{R}^{10}$, $\text{NR}^{10}\text{C}(\text{O})\text{C}(\text{O})\text{R}^{11}$,
 $\text{NR}^{10}\text{C}(\text{O})\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$, $\text{S}(\text{O})_2\text{R}^{10}$, $\text{S}(\text{O})_2\text{R}^{11}$, $\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{10}$, $\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{11}$,
 $\text{NR}^{10}\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{11}$, $\text{NR}^{10}\text{S}(\text{O})_2\text{R}^{10}$ or $\text{NR}^{10}\text{S}(\text{O})_2\text{R}^{11}$, provided that (1)
 one substituent is $\text{C}(\text{O})\text{R}^{10}$, COOR^{10} , $\text{C}(\text{O})\text{R}^{11}$, COOR^{11} ,
 5 $\text{C}(\text{O})\text{NR}^{10}\text{R}^{10}$, $\text{C}(\text{S})\text{NR}^{10}\text{R}^{10}$, $\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$, $\text{C}(\text{S})\text{NR}^{10}\text{R}^{11}$, $\text{NR}^{10}\text{C}(\text{O})\text{R}^{10}$,
 $\text{NR}^{10}\text{C}(\text{S})\text{R}^{10}$, $\text{NR}^{10}\text{C}(\text{O})\text{R}^{11}$, $\text{NR}^{10}\text{C}(\text{S})\text{R}^{11}$, $\text{NR}^{10}\text{C}(\text{O})\text{NR}^{10}\text{R}^{10}$,
 $\text{NR}^{10}\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$, $\text{NR}^{10}(\text{COOR}^{10})$, $\text{NR}^{10}(\text{COOR}^{11})$, $\text{NR}^{10}\text{C}(\text{S})\text{NR}^{10}\text{R}^{10}$,
 $\text{NR}^{10}\text{C}(\text{S})\text{NR}^{10}\text{R}^{11}$, $\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{10}$, $\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{11}$, $\text{NR}^{10}\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{11}$,
 $\text{NR}^{10}\text{S}(\text{O})_2\text{R}^{10}$ or $\text{NR}^{10}\text{S}(\text{O})_2\text{R}^{11}$;
 10 R^4 is H, halo, haloalkyl, NO_2 , CN, NR^7R^7 , OR^7 , SR^7 ,
 $\text{C}(\text{O})\text{R}^7$, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -
 cycloalkyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -
 alkynyl and C_{3-10} -cycloalkyl optionally comprising 1-4
 heteroatoms selected from N, O and S and optionally
 15 substituted with 1-3 substituents of R^9 ;
 R^5 is H, halo, haloalkyl, NO_2 , CN, NR^7R^7 , OR^7 , SR^7 ,
 $\text{C}(\text{O})\text{R}^7$, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -
 cycloalkyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -
 alkynyl and C_{3-10} -cycloalkyl optionally comprising 1-4
 20 heteroatoms selected from N, O and S and optionally
 substituted with 1-3 substituents of R^9 ;
 R^7 is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -
 cycloalkyl or C_{4-10} -cycloalkenyl, each of the C_{1-10} -alkyl, C_{2-}
 $_{10}$ -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl and C_{4-10} -
 25 cycloalkenyl optionally comprising 1-4 heteroatoms selected
 from N, O and S and optionally substituted with 1-3
 substituents of NR^8R^9 , NR^9R^9 , OR^8 , SR^8 , OR^9 , SR^9 , $\text{C}(\text{O})\text{R}^8$,
 $\text{OC}(\text{O})\text{R}^8$, COOR^8 , $\text{C}(\text{O})\text{R}^9$, $\text{OC}(\text{O})\text{R}^9$, COOR^9 , $\text{C}(\text{O})\text{NR}^8\text{R}^9$, $\text{C}(\text{O})\text{NR}^9\text{R}^9$,
 $\text{NR}^9\text{C}(\text{O})\text{R}^8$, $\text{NR}^9\text{C}(\text{O})\text{R}^9$, $\text{NR}^9\text{C}(\text{O})\text{NR}^8\text{R}^9$, $\text{NR}^9\text{C}(\text{O})\text{NR}^9\text{R}^9$, $\text{NR}^9(\text{COOR}^8)$,
 30 $\text{NR}^9(\text{COOR}^9)$, $\text{OC}(\text{O})\text{NR}^8\text{R}^9$, $\text{OC}(\text{O})\text{NR}^9\text{R}^9$, $\text{S}(\text{O})_2\text{R}^8$, $\text{S}(\text{O})_2\text{NR}^8\text{R}^9$,
 $\text{S}(\text{O})_2\text{R}^9$, $\text{S}(\text{O})_2\text{NR}^9\text{R}^9$, $\text{NR}^9\text{S}(\text{O})_2\text{NR}^8\text{R}^9$, $\text{NR}^9\text{S}(\text{O})_2\text{NR}^9\text{R}^9$, $\text{NR}^9\text{S}(\text{O})_2\text{R}^8$,
 $\text{NR}^9\text{S}(\text{O})_2\text{R}^9$, R^8 or R^9 ;
 R^8 is a partially or fully saturated or unsaturated 5-8
 membered monocyclic, 6-12 membered bicyclic, or 7-14

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membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and
5 wherein said ring system is optionally substituted independently with 1-5 substituents of R⁹, oxo, NR⁹R⁹, OR⁹, SR⁹, C(O)R⁹ or a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and optionally
10 substituted independently with 1-3 substituents of R⁹;
alternatively, R⁷ and R⁸ taken together form a saturated or partially or fully unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally
15 substituted independently with 1-3 substituents of R⁹;
R⁹ is H, halo, haloalkyl, CN, OH, NO₂, NH₂, acetyl, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl or a saturated or partially or
20 fully unsaturated 5-8 membered monocyclic or a 6-12 membered bicyclic, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, wherein each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl and ring of
25 said ring system is optionally substituted independently with 1-3 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamine, dimethylamine, ethylamine, diethylamine, propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;
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R^{10} is H, halo, haloalkyl, CN, NO_2 , C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl or C_{4-10} -cycloalkenyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl and C_{4-10} -cycloalkenyl optionally comprising 1-4
 5 heteroatoms selected from N, O and S and optionally substituted with 1-5 substituents of R^{11} , R^{12} or R^{16} , $NR^{11}R^{12}$, $NR^{12}R^{12}$, OR^{11} , SR^{11} , OR^{12} , SR^{12} , $C(O)R^{11}$, $OC(O)R^{11}$, $COOR^{11}$, $C(O)R^{12}$, $OC(O)R^{12}$, $COOR^{12}$, $C(O)NR^{11}R^{12}$, $NR^{12}C(O)R^{11}$, $C(O)NR^{12}R^{12}$, $NR^{12}C(O)R^{12}$, $NR^{12}C(O)NR^{11}R^{12}$, $NR^{12}C(O)NR^{12}R^{12}$, $NR^{12}(COOR^{11})$,
 10 $NR^{12}(COOR^{12})$, $OC(O)NR^{11}R^{12}$, $OC(O)NR^{12}R^{12}$, $S(O)_2R^{11}$, $S(O)_2R^{12}$, $S(O)_2NR^{11}R^{12}$, $S(O)_2NR^{12}R^{12}$, $NR^{12}S(O)_2NR^{11}R^{12}$, $NR^{12}S(O)_2NR^{12}R^{12}$, $NR^{12}S(O)_2R^{11}$, $NR^{12}S(O)_2R^{12}$, $NR^{12}S(O)_2R^{11}$ or $NR^{12}S(O)_2R^{12}$;

R^{11} is a partially or fully saturated or unsaturated 5-
 8 membered monocyclic, 6-12 membered bicyclic, or 7-14
 15 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein each ring of said ring system is optionally
 20 substituted independently with 1-5 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

alternatively, R^{10} and R^{11} taken together form a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms
 25 selected from O, N, or S, and the ring optionally substituted independently with 1-5 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which
 30 is optionally substituted independently with 1-5 substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} , SR^{14} , OR^{15} , SR^{15} , $C(O)R^{14}$, $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$,

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C(O)NR¹⁵R¹⁵, NR¹⁴C(O)R¹⁴, NR¹⁵C(O)R¹⁴, NR¹⁴C(O)R¹⁵, NR¹⁵C(O)R¹⁵,
NR¹⁵C(O)NR¹⁴R¹⁵, NR¹⁵C(O)NR¹⁵R¹⁵, NR¹⁵(COOR¹⁴), NR¹⁵(COOR¹⁵),
OC(O)NR¹⁴R¹⁵, OC(O)NR¹⁵R¹⁵, S(O)₂R¹⁴, S(O)₂R¹⁵, S(O)₂NR¹⁴R¹⁵,
S(O)₂NR¹⁵R¹⁵, NR¹⁴S(O)₂NR¹⁴R¹⁵, NR¹⁵S(O)₂NR¹⁵R¹⁵, NR¹⁴S(O)₂R¹⁴ or
5 NR¹⁵S(O)₂R¹⁵;

R¹⁴ is a partially or fully saturated or unsaturated 5-
8 membered or a saturated or partially or fully unsaturated
5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14
membered tricyclic ring system, said ring system formed of
10 carbon atoms optionally including 1-3 heteroatoms if
monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms
if tricyclic, said heteroatoms selected from O, N, or S, and
wherein each ring of said ring system is optionally
substituted independently with 1-5 substituents of R¹⁵ or
15 R¹⁶;

R¹⁵ is H or C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-
cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-
dialkylamino-, C₁₋₁₀-alkoxyl or C₁₋₁₀-thioalkoxyl, each of
which is optionally substituted independently with 1-5
20 substituents of R¹⁶;

R¹⁶ is H, halo, haloalkyl, CN, OH, NO₂, NH₂, OH, methyl,
methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl,
cyclopropyl, butyl, isobutyl, tert-butyl, methylamino,
dimethylamino, ethylamino, diethylamino, isopropylamino,
25 oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a
partially or fully saturated or unsaturated 5-8 membered
monocyclic or 6-12 membered bicyclic ring system, said ring
system formed of carbon atoms optionally including 1-3
heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic,
30 said heteroatoms selected from O, N, or S, and optionally
substituted independently with 1-5 substituents of halo,
haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl,
ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl,

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isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl;

- and provided that (1) when said at least one substituent on said R² ring system is C(O)NR¹⁰R¹⁰ or C(O)NR¹⁰R¹¹, then R¹⁰ and R¹¹, independently, are not -CH₂-L-Q or -C(C₁₋₆alkyl)(C₁₋₆alkyl)-L-Q, wherein L is -O-, -NH-, -NHC(O)-, -NHC(O)N-, -NHC(=NH)N- or -CO₂- and Q is H, substituted or unsubstituted C₁₋₆alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteraryl or C₁₋₆alkyl substituted with aryl, heterocyclyl or heteroaryl; or
- (2) when said R² is a phenyl ring substituted with C(O)NR¹⁰R¹⁰ or C(O)NR¹⁰R¹¹ meta to the point of attachment of the alkynyl group on R² of Formula I, then either (a) R¹ is not halogen, C₁₋₆alkyl, C₁₋₆alkoxyl or hydroxyl or (b) where R¹ and R³ taken together with the atoms to which they are attached form a partially or fully unsaturated 5- or 6-membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, said ring is not substituted with halogen, C₁₋₆alkyl, C₁₋₆alkoxyl or hydroxyl substituents.

In another embodiment, the compounds are generally defined by Formula I herein, wherein

- Each of A¹, A², A³, A⁴, R¹ are as defined in any of the embodiments above, and

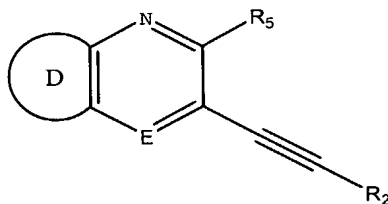
- R² is a partially or fully saturated 6-12 membered bicyclic or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms and including 1-6 heteroatoms if bicyclic or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, wherein said ring system is substituted independently with one or more substituents of R¹⁰, R¹¹, R¹⁵, NR¹⁰R¹⁰, NR¹⁰R¹¹, OR¹⁰, SR¹⁰, OR¹¹, SR¹¹, C(O)R¹⁰, C(S)R¹⁰, C(NCN)R¹⁰, C(O)R¹¹, C(S)R¹¹, C(NCN)R¹¹, C(O)C(O)R¹⁰, OC(O)R¹⁰, COOR¹⁰, C(O)SR¹⁰, C(O)C(O)R¹¹, OC(O)R¹¹,

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COOR¹¹, C(O)SR¹¹, C(O)NR¹⁰R¹⁰, C(S)NR¹⁰R¹⁰, C(O)NR¹⁰R¹¹,
 C(S)NR¹⁰R¹¹, OC(O)NR¹⁰R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(O)R¹¹, NR¹⁰C(S)R¹⁰,
 NR¹⁰C(S)R¹¹, NR¹⁰C(O)NR¹⁰R¹⁰, NR¹⁰C(O)NR¹⁰R¹¹, NR¹⁰C(S)NR¹⁰R¹⁰,
 NR¹⁰C(S)NR¹⁰R¹¹, NR¹⁰(COOR¹⁰), NR¹⁰(COOR¹¹), NR¹⁰C(O)C(O)R¹⁰,
 5 NR¹⁰C(O)C(O)R¹¹, NR¹⁰C(O)C(O)NR¹⁰R¹¹, S(O)₂R¹⁰, S(O)₂R¹¹,
 S(O)₂NR¹⁰R¹⁰, S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂R¹⁰ or
 NR¹⁰S(O)₂R¹¹, provided that (1) one substituent is C(O)R¹⁰,
 COOR¹⁰, C(O)R¹¹, COOR¹¹, C(O)NR¹⁰R¹⁰, C(S)NR¹⁰R¹⁰, C(O)NR¹⁰R¹¹,
 C(S)NR¹⁰R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(S)R¹⁰, NR¹⁰C(O)R¹¹, NR¹⁰C(S)R¹¹,
 10 NR¹⁰C(O)NR¹⁰R¹⁰, NR¹⁰C(O)NR¹⁰R¹¹, NR¹⁰(COOR¹⁰), NR¹⁰(COOR¹¹),
 NR¹⁰C(S)NR¹⁰R¹⁰, NR¹⁰C(S)NR¹⁰R¹¹, S(O)₂NR¹⁰R¹⁰, S(O)₂NR¹⁰R¹¹,
 NR¹⁰S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂R¹⁰ or NR¹⁰S(O)₂R¹¹, in conjunction
 with any of the above or below embodiments.

For example, in the embodiment immediately above, R²
 15 may be a quinolinyl, isoquinolinyl, quinazolinyl,
 isoquinazolinyl, phthalazinyl, aza-phthalazinyl,
 benzothiophenyl, benzofuryl, benzopyrazolyl, benzotriazolyl,
 benzothiazolyl, benzothiadiazolyl, benzoxazolyl,
 benzisoxazolyl, benzoxadiazolyl, benzisothiazolyl, indolyl,
 20 isoindolyl, dihydrobenzofuranyl or benzimidazolyl ring
 system.

In another embodiment, the compounds are generally
 defined by Formula III



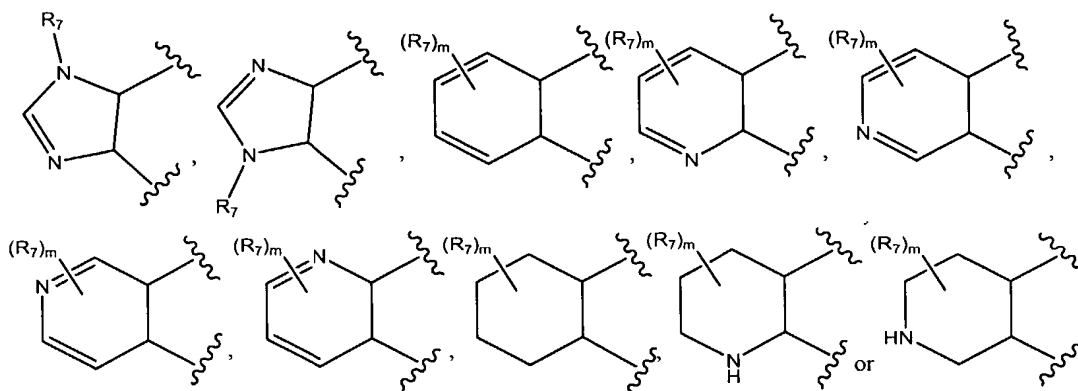
III

25

wherein

D is

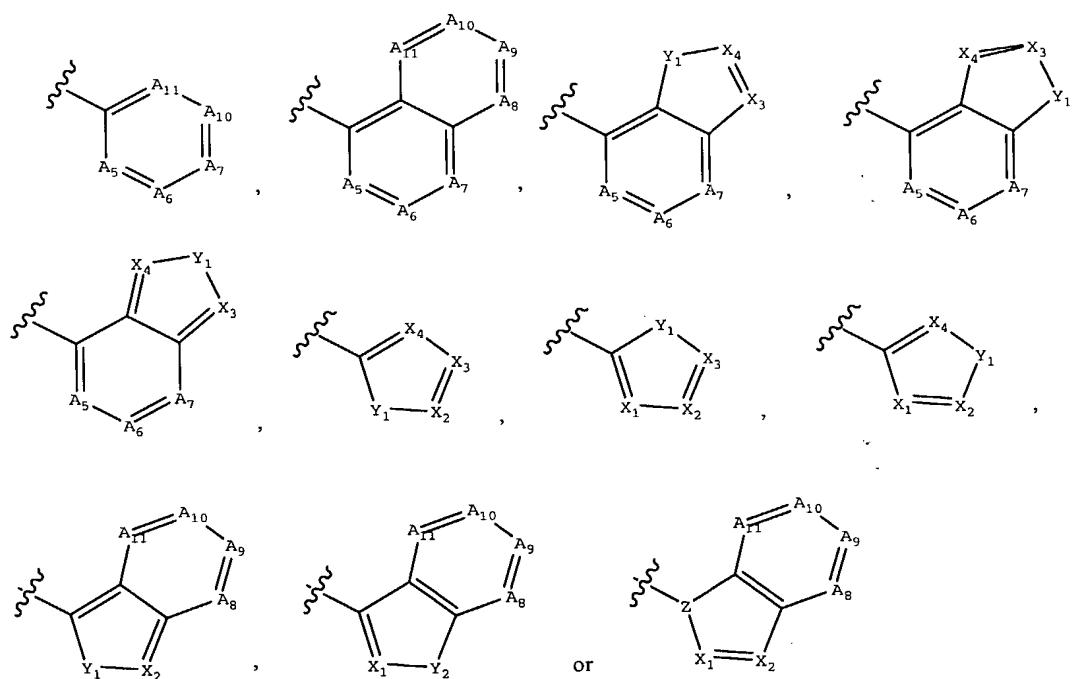
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wherein m is 0, 1, 2 or 3;

E is CR^4 or N ;

5 R^2 is



wherein

one of A^6 and A^7 is CR^{3a} and the other of A^6 and A^7 is CR^{3b} or N ;

10 each of A^5, A^8, A^9, A^{10} and A^{11} is, independently, CR^{3b} or N ;

X^2 is CR^{3a} ;

each of X^1, X^3 and X^4 is, independently, CR^{3b} or N ;

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Y^1 is $CR^{3b}R^{3c}$, NR^{3c} , O or S;

Y^2 is $CR^{3a}R^{3b}$ or NR^{3a} ; and

Z is CH or N;

R^{3a} is $C(O)OC_{1-3}$ -alkyl R^{11} , $OC(O)R^{11}$, $COOR^{11}$, $C(O)SC_{1-3}$ -alkyl R^{11} , $C(O)SR^{11}$, $C(O)N(R^{10})C_{1-3}$ -alkyl R^{11} , $C(S)N(R^{10})C_{1-3}$ -alkyl R^{11} , $C(O)NR^{10}R^{11}$, $C(S)NR^{10}R^{11}$, $NR^{10}C(O)C_{1-3}$ -alkyl R^{11} , $NR^{10}C(S)C_{1-3}$ -alkyl R^{11} , $NR^{10}C(O)R^{11}$, $NR^{10}C(S)R^{11}$, $NR^{10}C(O)N(R^{10})C_{1-3}$ -alkyl R^{11} , $NR^{10}C(O)NR^{10}R^{11}$, $NR^{10}C(S)N(R^{10})C_{1-3}$ -alkyl R^{11} , $NR^{10}C(S)NR^{10}R^{11}$, $NR^{10}C(O)OC_{1-3}$ -alkyl R^{11} , $NR^{10}(COOR^{11})$, $OC(O)NR^{10}R^{11}$, $S(O)_2N(R^{10})C_{1-3}$ -alkyl R^{11} , $S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2C_{1-3}$ -alkyl R^{11} or $NR^{10}S(O)_2R^{11}$;

R^{3b} is H, halo, haloalkyl, CN, NO_2 , NH_2 , C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl; and

R^{3c} is H, CN or C_{1-10} -alkyl;

R^4 is H, halo, haloalkyl, NO_2 , CN, OH, O- C_{1-10} -alkyl, NH_2 , C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl;

R^5 is H, halo, haloalkyl, NO_2 , CN, OH, NH_2 , O- C_{1-10} -alkyl, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl;

Each R^7 , independently, is H, R^8 , C_{1-10} -alkyl, C_{2-10} -alkenyl or C_{2-10} -alkynyl, each of which is optionally substituted with 1-3 substituents of NR^8R^9 , NR^9R^9 , OR^8 , SR^8 , OR^9 , SR^9 , $C(O)R^8$, $C(O)R^9$, $C(O)NR^8R^9$, $C(O)NR^9R^9$, $S(O)_2R^8$, $S(O)_2NR^8R^9$, $S(O)_2R^9$, $S(O)_2NR^9R^9$, R^8 or R^9 ;

R^8 is a ring system selected from phenyl, pyridyl, piperazinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrrolidinyl, oxazolinyl, isoxazolinyl, thiazolinyl, pyrazolinyl, morpholinyl, piperidinyl, pyranal, dioxozinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, said ring system optionally substituted

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independently with 1-3 substituents of R^9 , oxo, NR^9R^9 , OR^9 , SR^9 or $C(O)R^9$;

- R^9 is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , acetyl, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl, C_{1-10} -thioalkoxyl or a ring system selected from phenyl, naphthyl, pyridyl, piperazinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuranyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, morpholyl, piperidinyl, piperazinyl, pyranyl, dioxozinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl, C_{1-10} -thioalkoxyl and ring system optionally substituted independently with 1-3 substituents of halo, haloalkyl, CN, NO_2 , NH_2 , OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;
- R^{10} is H, CN, NO_2 , C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl or C_{4-10} -cycloalkenyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl and C_{4-10} -cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents of R^{11} , R^{12} or R^{16} , $NR^{11}R^{12}$, $NR^{12}R^{12}$, OR^{11} , SR^{11} , OR^{12} , SR^{12} , $C(O)R^{11}$, $OC(O)R^{11}$, $COOR^{11}$, $C(O)R^{12}$, $OC(O)R^{12}$, $COOR^{12}$, $C(O)NR^{11}R^{12}$, $NR^{12}C(O)R^{11}$, $C(O)NR^{12}R^{12}$, $NR^{12}C(O)R^{12}$, $NR^{12}C(O)NR^{11}R^{12}$, $NR^{12}C(O)NR^{12}R^{12}$, $NR^{12}(COOR^{11})$, $NR^{12}(COOR^{12})$, $OC(O)NR^{11}R^{12}$, $OC(O)NR^{12}R^{12}$, $S(O)_2R^{11}$, $S(O)_2R^{12}$, $S(O)_2NR^{11}R^{12}$,

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$S(O)_2NR^{12}R^{12}$, $NR^{12}S(O)_2NR^{11}R^{12}$, $NR^{12}S(O)_2NR^{12}R^{12}$, $NR^{12}S(O)_2R^{11}$,
 $NR^{12}S(O)_2R^{12}$, $NR^{12}S(O)_2R^{11}$ or $NR^{12}S(O)_2R^{12}$;

R^{11} is a phenyl, naphthyl, 5,6,7,8-tetrahydronaphthyl,
dihydro-indenyl, pyridyl, pyrimidinyl, triazinyl,
5 quinolinyl, tetrahydroquinolinyl, oxo-tetrahydroquinolinyl,
isoquinolinyl, oxo-tetrahydroisoquinolinyl,
tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl,
thiophenyl, furyl, tetrahydrofuranlyl, pyrrolyl, pyrazolyl,
thieno-pyrazolyl, tetrahydropentapyrazolyl, imidazolyl,
10 triazolyl, tetrazolyl, thiazolyl, thiadiazolyl,
benzothiazolyl, oxazolyl, oxadiazolyl, benzoxazolyl,
benzoxadiazolyl, isoxazolyl, isothiazolyl, indolyl,
azaindolyl, 2,3-dihydroindolyl, isoindolyl, indazolyl,
benzofuranlyl, benzothiophenyl, benzimidazolyl, imidazo-
15 pyridinyl, purinyl, benzotriazolyl, oxazolinyl,
isoxazolinyl, thiazolinyl, pyrrolidinyl, pyrazolinyl,
morpholinyl, piperidinyl, piperazinyl, pyranlyl, dioxozinyl,
2,3-dihydro-1,4-benzoxazinyl, 1,3-benzodioxolyl,
cyclopropyl, cyclobutyl, azetidiny, cyclopentyl, cyclohexyl
20 or cycloheptyl ring system, said ring system optionally
substituted independently with 1-3 substituents of R^{12} , R^{13} ,
 R^{14} or R^{16} ;

alternatively, R^{10} and R^{11} taken together form a
partially or fully saturated or unsaturated 5-6 membered
25 ring of carbon atoms optionally including 1-3 heteroatoms
selected from O, N, or S, and the ring optionally
substituted independently with 1-3 substituents of R^{12} , R^{13} ,
 R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -
30 cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -
dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which
is optionally substituted independently with 1-3
substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

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R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} , SR^{14} , OR^{15} , SR^{15} , $C(O)R^{14}$, $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$, $C(O)NR^{15}R^{15}$, $NR^{14}C(O)R^{14}$, $NR^{15}C(O)R^{14}$, $NR^{14}C(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(O)NR^{14}R^{15}$, $NR^{15}C(O)NR^{15}R^{15}$, $NR^{15}(COOR^{14})$, $NR^{15}(COOR^{15})$,
 5 $OC(O)NR^{14}R^{15}$, $OC(O)NR^{15}R^{15}$, $S(O)_2R^{14}$, $S(O)_2R^{15}$, $S(O)_2NR^{14}R^{15}$, $S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2NR^{14}R^{15}$, $NR^{15}S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2R^{14}$ or $NR^{15}S(O)_2R^{15}$;

R^{14} is phenyl, pyridyl, pyrimidinyl, thiophenyl, furyl, tetrahydrofuryl, pyrrolyl, pyrazolyl, thieno-pyrazolyl,
 10 imidazolyl, triazolyl, thiazolyl, thiadiazolyl, benzothiazolyl, oxazolyl, oxadiazolyl, benzoxazolyl, benzoxadiazolyl, isoxazolyl, isothiazolyl, indolyl, azaindolyl, isoindolyl, indazolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, pyrrolidinyl, pyrazolinyl,
 15 morpholinyl, piperidinyl, piperazinyl, 2,3-dihydro-1,4-benzoxazinyl, 1,3-benzodioxolyl, cyclopropyl, cyclobutyl, azetidyl, cyclopentyl and cyclohexyl, each of which is optionally substituted independently with 1-3 substituents of R^{15} or R^{16} ;

R^{15} is H or C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkoxyl, each of which is optionally substituted independently with 1-3 substituents of R^{16} ; and

R^{16} is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a
 25 partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally
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substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

In other embodiments, Formulas I, II and III include various of the exemplary compounds described in the Experimental Methods section hereinbelow.

DEFINITIONS

The following definitions should assist in understanding the invention described herein.

The terms "agonist" and "agonistic" when used herein refer to or describe a molecule which is capable of, directly or indirectly, substantially inducing, promoting or enhancing biological activity of a biological molecule, such as an enzyme or receptor, including Tie-2 and Lck.

The term "comprising" is meant to be open ended, including the indicated component(s), but not excluding other elements.

The term "H" denotes a single hydrogen atom. This radical may be attached, for example, to an oxygen atom to form a hydroxyl radical.

The term "C_{α-β}alkyl", when used either alone or within other terms such as "haloalkyl" and "alkylamino", embraces linear or branched radicals having α to β number of carbon atoms (such as C₁-C₁₀).

The term "alkyl" radicals include "lower alkyl" radicals having one to about six carbon atoms. Examples of such radicals include methyl, ethyl, n-propyl, isopropyl, n-butyl, isobutyl, sec-butyl, tert-butyl, pentyl, isoamyl, hexyl and the like. The term "alkylenyl" embraces bridging divalent alkyl radicals such as methylenyl and ethylenyl.

The term "alkenyl", when used alone or in combination, embraces linear or branched radicals having at least one

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carbon-carbon double bond in a moiety having between two and ten carbon atoms. Included within alkenyl radicals are "lower alkenyl" radicals having two to about six carbon atoms and, for example, those radicals having two to about
5 four carbon atoms. Examples of alkenyl radicals include, without limitation, ethenyl, propenyl, allyl, propenyl, butenyl and 4-methylbutenyl. The terms "alkenyl" and "lower alkenyl", embrace radicals having "cis" and "trans" orientations, or alternatively, "E" and "Z" orientations, as
10 appreciated by those of ordinary skill in the art.

The term "alkynyl", when used alone or in combination, denotes linear or branched radicals having at least one carbon-carbon triple bond and having two to ten carbon atoms. Examples of alkynyl radicals include "lower alkynyl"
15 radicals having two to about six carbon atoms and, for example, lower alkynyl radicals having two to about four carbon atoms. Examples of such radicals include, without limitation, ethynyl, propynyl (propargyl), butynyl, and the like.

20 The term "alkoxy" or "alkoxyl", when used alone or in combination, embraces linear or branched oxygen-containing radicals each having alkyl portions of one or more carbon atoms. The term alkoxy radicals include "lower alkoxy" radicals having one to six carbon atoms. Examples of such
25 radicals include methoxy, ethoxy, propoxy, butoxy and tert-butoxy. Alkoxy radicals may be further substituted with one or more halo atoms, such as fluoro, chloro or bromo, to provide "haloalkoxy" radicals. Examples of such radicals include fluoromethoxy, chloromethoxy, trifluoromethoxy,
30 trifluoroethoxy, fluoroethoxy and fluoropropoxy.

The term "aryl", when used alone or in combination, means a carbocyclic aromatic moiety containing one, two or even three rings wherein such rings may be attached together in a fused manner. Every ring of an "aryl" ring system need

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not be aromatic, and the ring(s) fused to the aromatic ring may be partially or fully unsaturated and include one or more heteroatoms selected from nitrogen, oxygen and sulfur. Thus, the term "aryl" embraces aromatic radicals such as phenyl, naphthyl, indenyl, tetrahydronaphthyl, dihydrobenzafuranyl, anthracenyl, indanyl, benzodioxazinyl, and the like. The "aryl" group may be substituted, such as with 1 to 5 substituents including lower alkyl, hydroxyl, halo, haloalkyl, nitro, cyano, alkoxy and lower alkylamino, and the like. Phenyl substituted with -O-CH₂-O- or -O-CH₂-CH₂-O- forms an aryl benzodioxolyl substituent.

The term "carbocyclic", also referred to herein as "cycloalkyl", when used alone or in combination, means a partially or fully saturated ring moiety containing one ("monocyclic"), two ("bicyclic") or even three ("tricyclic") rings wherein such rings may be attached together in a fused manner and formed from carbon atoms. Examples of saturated carbocyclic radicals include saturated 3 to 6-membered monocyclic groups such as cyclopropane, cyclobutane, cyclopentane and cyclohexane.

The term "cycloalkenyl", when used alone or in combination, means a partially or fully saturated cycloalkyl containing one, two or even three rings in a structure having at least one carbon-carbon double bond in the structure. Examples of cycloalkenyl groups include C₃-C₆ rings, such as compounds including, without limitation, cyclopropene, cyclobutene, cyclopentene and cyclohexene. The term also includes carbocyclic groups having two or more carbon-carbon double bonds such as "cycloalkyldienyl" compounds. Examples of cycloalkyldienyl groups include, without limitation, cyclopentadiene and cycloheptadiene.

The term "halo", when used alone or in combination, means halogens such as fluorine, chlorine, bromine or iodine atoms.

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The term "haloalkyl", when used alone or in combination, embraces radicals wherein any one or more of the alkyl carbon atoms is substituted with halo as defined above. For example, this term includes monohaloalkyl, dihaloalkyl and polyhaloalkyl radicals such as a perhaloalkyl. A monohaloalkyl radical, for example, may have either an iodo, bromo, chloro or fluoro atom within the radical. Dihalo and polyhaloalkyl radicals may have two or more of the same halo atoms or a combination of different halo radicals. "Lower haloalkyl" embraces radicals having 1-6 carbon atoms and, for example, lower haloalkyl radicals having one to three carbon atoms. Examples of haloalkyl radicals include fluoromethyl, difluoromethyl, trifluoromethyl, chloromethyl, dichloromethyl, trichloromethyl, pentafluoroethyl, heptafluoropropyl, difluorochloromethyl, dichlorofluoromethyl, difluoroethyl, difluoropropyl, dichloroethyl and dichloropropyl. "Perfluoroalkyl", as used herein, refers to alkyl radicals having all hydrogen atoms replaced with fluoro atoms. Examples include trifluoromethyl and pentafluoroethyl.

The term "ring system" refers generally to a moiety comprising one or more rings collectively having the delineated number of atoms, the atoms being carbon or, where indicated, a heteroatom such as nitrogen, oxygen or sulfur. The ring itself, as well as any substituents thereon, may be attached at any atom that allows a stable compound to be formed. The term "nonaromatic" ring or ring system refers to the fact that at least one, but not necessarily all, rings in a bicyclic or tricyclic ring system is nonaromatic.

The term "heteroaryl", as used herein, either alone or in combination, means a fully unsaturated (aromatic) ring moiety formed from carbon atoms and having one or more heteroatoms selected from nitrogen, oxygen and sulfur. The ring moiety or ring system may contain one ("monocyclic"),

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two ("bicyclic") or even three ("tricyclic") rings wherein such rings are attached together in a fused manner. Every ring of a "heteroaryl" ring system need not be aromatic, and the ring(s) fused thereto (to the heteroaromatic ring) may
5 be partially or fully saturated and optionally include one or more heteroatoms selected from nitrogen, oxygen and sulfur. The term "heteroaryl" does not include rings having ring members of -O-O-, -O-S- or -S-S-.

Examples of unsaturated heteroaryl radicals, include
10 unsaturated 5- to 6- membered heteromonocyclyl groups containing 1 to 4 nitrogen atoms, including for example, pyrrolyl, imidazolyl, pyrazolyl, 2-pyridyl, 3-pyridyl, 4-pyridyl, pyrimidyl, pyrazinyl, pyridazinyl, triazolyl [e.g., 4H-1,2,4-triazolyl, 1H-1,2,3-triazolyl, 2H-1,2,3-triazolyl]
15 and tetrazole; unsaturated 7- to 10- membered heterobicyclyl groups containing 1 to 4 nitrogen atoms, including for example, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, aza-quinazolinyl, and the like; unsaturated 5- to 6-membered heteromonocyclic group containing an oxygen
20 atom, for example, pyranyl, 2-furyl, 3-furyl, benzofuryl, etc.; unsaturated 5 to 6-membered heteromonocyclic group containing a sulfur atom, for example, 2-thienyl, 3-thienyl, benzothienyl, etc.; unsaturated 5- to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1
25 to 3 nitrogen atoms, for example, oxazolyl, isoxazolyl, oxadiazolyl [e.g., 1,2,4-oxadiazolyl, 1,3,4-oxadiazolyl, 1,2,5-oxadiazolyl]; unsaturated 5 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms, for example, thiazolyl, isothiazolyl,
30 thiadiazolyl [e.g., 1,2,4-thiadiazolyl, 1,3,4-thiadiazolyl, 1,2,5-thiadiazolyl].

The term "heterocyclic", when used alone or in combination, means a partially or fully saturated ring moiety containing one, two or even three rings wherein such

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rings may be attached together in a fused manner, formed from carbon atoms and including one or more heteroatoms selected from N, O or S. Examples of saturated heterocyclic radicals include saturated 3 to 6-membered heteromonocyclic groups containing 1 to 4 nitrogen atoms [e.g. pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, piperazinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. morpholinyl]; saturated 3 to 6-membered heteromonocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., thiazolidinyl]. Examples of partially saturated heterocyclyl radicals include dihydrothienyl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl.

The term "heterocycle" also embraces radicals where heterocyclic radicals are fused/condensed with aryl or heteroaryl radicals: unsaturated condensed heterocyclic group containing 1 to 5 nitrogen atoms, for example, indolyl, isoindolyl, indoliziny, benzimidazolyl, quinolyl, isoquinolyl, indazolyl, benzotriazolyl, tetrazolopyridazinyl [e.g., tetrazolo [1,5-b]pyridazinyl]; unsaturated condensed heterocyclic group containing 1 to 2 oxygen atoms and 1 to 3 nitrogen atoms [e.g. benzoxazolyl, benzoxadiazolyl]; unsaturated condensed heterocyclic group containing 1 to 2 sulfur atoms and 1 to 3 nitrogen atoms [e.g., benzothiazolyl, benzothiadiazolyl]; and saturated, partially unsaturated and unsaturated condensed heterocyclic group containing 1 to 2 oxygen or sulfur atoms [e.g. benzofuryl, benzothienyl, 2,3-dihydro-benzo[1,4]dioxinyl and dihydrobenzofuryl]. Examples of heterocyclic radicals include five to ten membered fused or unfused radicals.

Examples of partially saturated and saturated heterocyclyl include, without limitation, pyrrolidinyl, imidazolidinyl, piperidinyl, pyrrolinyl, pyrazolidinyl, piperazinyl, morpholinyl, tetrahydropyranyl, thiazolidinyl,

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dihydrothienyl, 2,3-dihydro-benzo[1,4]dioxanyl, indolinyl, isoindolinyl, dihydrobenzothienyl, dihydrobenzofuryl, isochromanyl, chromanyl, 1,2-dihydroquinolyl, 1,2,3,4-tetrahydro-isoquinolyl, 1,2,3,4-tetrahydro-quinolyl, 2,3,4,4a,9,9a-hexahydro-1H-3-aza-fluorenyl, 5,6,7-trihydro-1,2,4-triazolo[3,4-a]isoquinolyl, 3,4-dihydro-2H-benzo[1,4]oxazinyl, benzo[1,4]dioxanyl, 2,3-dihydro-1H-1λ'-benzo[d]isothiazol-6-yl, dihydropyranyl, dihydrofuryl and dihydrothiazolyl, and the like.

10 The term "alkylamino" includes "N-alkylamino" where amino radicals are independently substituted with one alkyl radical. Preferred alkylamino radicals are "lower alkylamino" radicals having one to six carbon atoms. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Examples of such lower alkylamino radicals include N-methylamino, and N-ethylamino, N-propylamino, N-isopropylamino and the like.

20 The term "dialkylamino" includes "N, N-dialkylamino" where amino radicals are independently substituted with two alkyl radicals. Preferred alkylamino radicals are "lower alkylamino" radicals having one to six carbon atoms. Even more preferred are lower alkylamino radicals having one to three carbon atoms. Examples of such lower alkylamino radicals include N,N-dimethylamino, N,N-diethylamino, and the like.

25 The terms "carboxy" or "carboxyl", whether used alone or with other terms, such as "carboxyalkyl", denotes -CO₂H.

 The term "carbonyl", whether used alone or with other terms, such as "aminocarbonyl", denotes -(C=O)-.

30 The term "aminocarbonyl" denotes an amide group of the formula -C(=O)NH₂.

 The term "alkylthio" embraces radicals containing a linear or branched alkyl radical, of one to ten carbon

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atoms, attached to a divalent sulfur atom. An example of "alkylthio" is methylthio, (CH₃S-).

The term "haloalkylthio" embraces radicals containing a haloalkyl radical, of one to ten carbon atoms, attached to a divalent sulfur atom. An example of "haloalkylthio" is trifluoromethylthio.

The term "aminoalkyl" embraces linear or branched alkyl radicals having one to about ten carbon atoms any one of which may be substituted with one or more amino radicals. Examples of aminoalkyl radicals include "lower aminoalkyl" radicals having one to six carbon atoms and one or more amino radicals. Examples of such radicals include aminomethyl, aminoethyl, aminopropyl, aminobutyl and aminohexyl. Even more preferred are lower aminoalkyl radicals having one to three carbon atoms.

The term "alkylaminoalkyl" embraces alkyl radicals substituted with alkylamino radicals. Examples of alkylaminoalkyl radicals include "lower alkylaminoalkyl" radicals having alkyl radicals of one to six carbon atoms. Suitable alkylaminoalkyl radicals may be mono or dialkyl substituted, such as N-methylaminomethyl, N,N-dimethylaminoethyl, N,N-diethylaminomethyl and the like.

The term "alkylaminoalkoxy" embraces alkoxy radicals substituted with alkylamino radicals. Examples of alkylaminoalkoxy radicals include "lower alkylaminoalkoxy" radicals having alkoxy radicals of one to six carbon atoms. Suitable alkylaminoalkoxy radicals may be mono or dialkyl substituted, such as N-methylaminoethoxy, N,N-dimethylaminoethoxy, N,N-diethylaminoethoxy and the like.

The term "Formula I" includes any sub formulas, such as Formula II. Similarly, the terms "Formula II" and "Formula III" include any sub formulas.

The term "pharmaceutically-acceptable" when used with reference to a compound of Formulas I - III is intended to

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refer to a form of the compound that is safe for administration. For example, a salt form, a solvate, a hydrate or derivative form of a compound of Formula I, II or III, which has been approved for mammalian use, via oral
5 ingestion or other routes of administration, by a governing body or regulatory agency, such as the Food and Drug Administration (FDA) of the United States, is pharmaceutically acceptable.

Included in the compounds of Formulas I - III are the
10 pharmaceutically acceptable salt forms of the free-base compounds. The term "pharmaceutically-acceptable salts" embraces salts commonly used to form alkali metal salts and to form addition salts of free acids or free bases. As appreciated by those of ordinary skill in the art, salts may
15 be formed from ionic associations, charge-charge interactions, covalent bonding, complexation, coordination, etc. The nature of the salt is not critical, provided that it is pharmaceutically acceptable.

Suitable pharmaceutically acceptable acid addition
20 salts of compounds of Formulas I - III may be prepared from an inorganic acid or from an organic acid. Examples of such inorganic acids are hydrochloric, hydrobromic, hydroiodic, hydrofluoric, nitric, carbonic, sulfuric and phosphoric acid. Appropriate organic acids may be selected from
25 aliphatic, cycloaliphatic, aromatic, arylaliphatic, heterocyclic, carboxylic and sulfonic classes of organic acids, examples of which include, without limitation, formic, acetic, adipic, butyric, propionic, succinic, glycolic, gluconic, lactic, malic, tartaric, citric,
30 ascorbic, glucuronic, maleic, fumaric, pyruvic, aspartic, glutamic, benzoic, anthranilic, mesylic, 4-hydroxybenzoic, phenylacetic, mandelic, embonic (pamoic), methanesulfonic, ethanesulfonic, ethanedisulfonic, benzenesulfonic, pantothenic, 2-hydroxyethanesulfonic, toluenesulfonic,

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sulfanilic, cyclohexylaminosulfonic, camphoric, camphorsulfonic, digluconic, cyclopentanepropionic, dodecylsulfonic, glucoheptanoic, glycerophosphonic, heptanoic, hexanoic, 2-hydroxy-ethanesulfonic, nicotinic, 2-naphthalenesulfonic, oxalic, palmoic, pectinic, persulfuric, 2-phenylpropionic, picric, pivalic propionic, succinic, thiocyanic, undecanoic, stearic, algenic, β -hydroxybutyric, salicylic, galactaric and galacturonic acid. Suitable pharmaceutically-acceptable base addition salts of compounds of Formulas I - III include metallic salts, such as salts made from aluminum, calcium, lithium, magnesium, potassium, sodium and zinc, or salts made from organic bases including, without limitation, primary, secondary and tertiary amines, substituted amines including cyclic amines, such as caffeine, arginine, diethylamine, N-ethyl piperidine, histidine, glucamine, isopropylamine, lysine, morpholine, N-ethyl morpholine, piperazine, piperidine, triethylamine, diisopropylethylamine and trimethylamine. All of these salts may be prepared by conventional means from the corresponding compound of the invention by reacting, for example, the appropriate acid or base with the compound of Formulas I, II or III.

Also, the basic nitrogen-containing groups can be quaternized with such agents as lower alkyl halides, such as methyl, ethyl, propyl, and butyl chloride, bromides and iodides; dialkyl sulfates like dimethyl, diethyl, dibutyl, and diamyl sulfates, long chain halides such as decyl, lauryl, myristyl and stearyl chlorides, bromides and iodides, aralkyl halides like benzyl and phenethyl bromides, and others. Water or oil-soluble or dispersible products are thereby obtained.

Examples of acids that may be employed to form pharmaceutically acceptable acid addition salts include such inorganic acids as hydrochloric acid, hydrobromic acid,

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citric acid, sulphuric acid and phosphoric acid and such organic acids as oxalic acid, stearic and, salicylic acid, pamoic acid, gluconic acid, ethanesulfonic acid, methanesulfonic acid, toluenesulfonic acid, tartaric acid, fumaric acid, medronic acid, napsylic acid, maleic acid, succinic acid and citric acid. Other examples include salts with alkali metals or alkaline earth metals such as sodium, potassium, calcium or magnesium, or with organic bases.

Additional examples of such salts can be found in Berge et al., J. Pharm. Sci., 66, 1 (1977). Conventional methods may be used to form the salts. For example, a phosphate salt of a compound of the invention may be made by combining the desired compound free base in a desired solvent, or combination of solvents, with phosphoric acid in a desired stoichiometric amount, at a desired temperature, typically under heat (depending upon the boiling point of the solvent). The salt can be precipitated upon cooling (slow or fast) and may crystallize (i.e., if crystalline in nature), as appreciated by those of ordinary skill in the art. Further, hemi-, mono-, di, tri- and poly-salt forms of the compounds of the present invention are also contemplated herein. Similarly, hemi-, mono-, di, tri- and poly-hydrated forms of the compounds, salts and derivatives thereof, are also contemplated herein.

The term "derivative" is broadly construed herein, and intended to encompass any salt of a compound of this invention, any ester of a compound of this invention, or any other compound, which upon administration to a patient is capable of providing (directly or indirectly) a compound of this invention, or a metabolite or residue thereof, characterized by the ability to the ability to modulate a kinase enzyme.

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The term "pharmaceutically-acceptable derivative" as used herein, denotes a derivative which is pharmaceutically acceptable.

5 The term "prodrug", as used herein, denotes a compound which upon administration to a subject or patient is capable of providing (directly or indirectly) a compound of this invention. Examples of prodrugs would include esterified or hydroxylated compounds where the ester or hydroxyl groups would cleave in vivo, such as in the gut, to produce a
10 compound according to Formulas I - III. A "pharmaceutically-acceptable prodrug" as used herein, denotes a prodrug which is pharmaceutically acceptable. Pharmaceutically acceptable modifications to the compounds of Formulas I - III are readily appreciated by those of ordinary skill in the art.

15 The compound(s) of Formula I, II or III may be used to treat a subject by administering the compound(s) as a pharmaceutical composition. To this end, the compound(s) can be combined with one or more carriers, diluents or adjuvants to form a suitable composition, which is described in more
20 detail herein.

The term "carrier", as used herein, denotes any pharmaceutically acceptable additive, excipient, adjuvant, or other suitable ingredient, other than the active pharmaceutical ingredient (API), which is typically included
25 for formulation and/or administration purposes. "Diluent" and "adjuvant" are defined hereinafter.

The terms "treat", "treating," "treatment," and "therapy" as used herein refer to therapy, including without limitation, curative therapy, prophylactic therapy, and
30 preventative therapy. Prophylactic treatment generally constitutes either preventing the onset of disorders altogether or delaying the onset of a pre-clinically evident stage of disorders in individuals.

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The phrase "effective dosage amount" is intended to quantify the amount of each agent, which will achieve the goal of improvement in disorder severity and the frequency of incidence over treatment of each agent by itself, while
5 avoiding adverse side effects typically associated with alternative therapies. As such, this term is not limited to a single unit dosage, to be effective. Accordingly, it is contemplated herein that an "effective dosage amount" may include more than one unit dosage to be administered to the
10 subject. For example, the subject may be prescribed, or requested by qualifie medical staff, to ingest 2 tablets, which comprise a compound of the invention, to obtain an effective dosage amount.

The term "leaving groups" generally refer to groups
15 that are displaceable by a nucleophile. Such leaving groups are known in the art. Examples of leaving groups include, but are not limited to, halides (e.g., I, Br, F, Cl), sulfonates (e.g., mesylate, tosylate), sulfides (e.g., SCH₃), N-hydroxsuccinimide, N-hydroxybenzotriazole, and the
20 like. Nucleophiles are species that are capable of attacking a molecule at the point of attachment of the leaving group causing displacement of the leaving group. Nucleophiles are known in the art. Examples of nucleophilic groups include, but are not limited to, amines, thiols, alcohols, Grignard
25 reagents, anionic species (e.g., alkoxides, amides, carbanions) and the like.

The term "angiogenesis" is defined as any alteration of an existing vascular bed or the formation of new vasculature which benefits tissue perfusion. This includes
30 the formation of new vessels by sprouting of endothelial cells from existing blood vessels or the remodeling of existing vessels to alter size, maturity, direction and/or flow properties to improve blood perfusion of tissue.

The terms "cancer" and "cancerous" when used herein
35 refer to or describe the physiological condition in mammals

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that is typically characterized by unregulated cell growth. Examples of cancer include, without limitation, carcinoma, lymphoma, sarcoma, blastoma and leukemia. More particular examples of such cancers include squamous cell carcinoma, lung cancer, pancreatic cancer, cervical cancer, bladder cancer, hepatoma, breast cancer, colon carcinoma, and head and neck cancer. While the term "cancer" as used herein is not limited to any one specific form of the disease, it is believed that the methods of the invention will be particularly effective for cancers which are found to be accompanied by unregulated levels of Tie-2, and similar kinases, in the subject.

GENERAL SYNTHETIC PROCEDURES

The present invention further comprises procedures for the preparation of a compound of Formulas I - III. The compounds of Formulas I - III can be synthesized according to the procedures described in the following Schemes 1-6, wherein the substituents are generally as defined for Formulas I - III above, except where further noted. The synthetic methods described below are merely exemplary, and the compounds of the invention may be synthesized by alternate routes as appreciated by persons of ordinary skill in the art.

The following list of abbreviations used throughout the specification represent the following and should assist in understanding the invention:

ACN, MeCN	-	acetonitrile
BSA	-	bovine serum albumin
Cs ₂ CO ₃	-	cesium carbonate
CHCl ₃	-	chloroform
CH ₂ Cl ₂ , DCM	-	dichloromethane, methylene chloride
CuBr	-	copper bromide
CuI	-	copper iodide

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	DIBAL	-	diisobutylaluminum hydride
	DIC	-	1,3-diisopropylcarbodiimide
	DIEA, (iPr) ₂ NEt	-	diisopropylethylamine
	DME	-	dimethoxyethane
5	DMF	-	dimethylformamide
	DMAP	-	4-dimethylaminopyridine
	DMSO	-	dimethylsulfoxide
	EDC	-	1-(3-dimethylaminopropyl)-3-ethylcarbodiimide
10	Et ₂ O	-	diethyl ether
	EtOAc	-	ethyl acetate

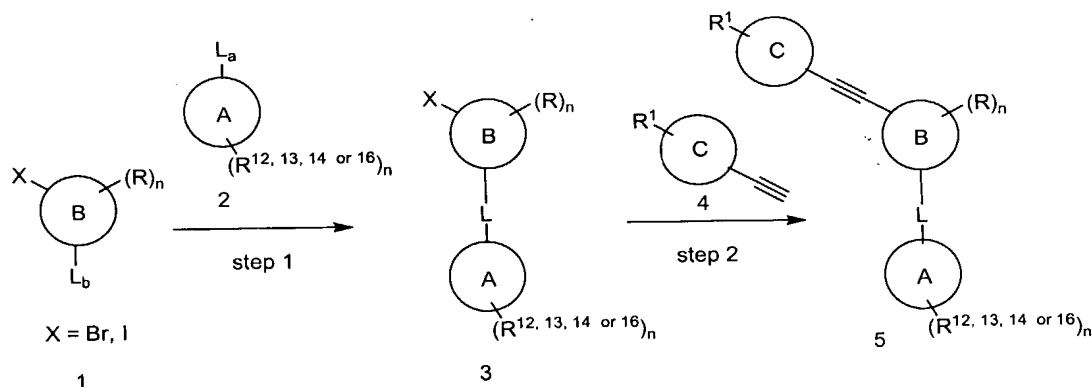
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	FBS	-	fetal bovine serum
	G, gm	-	gram
	h, hr	-	hour
	H ₂	-	hydrogen
5	HATU	-	O-(7-azabenzotriazol-1-yl)-N,N,N',N'-tetramethyluroniumhexafluorophosphate
	HBr	-	hydrobromic acid
	HCl	-	hydrochloric acid
	HOBt	-	1-hydroxybenzotriazole hydrate
10	HPLC	-	high pressure liquid chromatography
	IPA, IpOH	-	isopropyl alcohol
	K ₂ CO ₃	-	potassium carbonate
	KI	-	potassium iodide
	MgSO ₄	-	magnesium sulfate
15	MeOH	-	methanol
	N ₂	-	nitrogen
	NaCNBH ₃	-	sodium cyanoborohydride
	NaHCO ₃	-	sodium bicarbonate
	NaH	-	sodium hydride
20	NaOCH ₃	-	sodium methoxide
	NaOH	-	sodium hydroxide
	Na ₂ SO ₄	-	sodium sulfate
	NH ₄ Cl	-	ammonium chloride
	NH ₄ OH	-	ammonium hydroxide
25	NMP	-	N-methylpyrrolidinone
	P(<i>t</i> -bu) ₃	-	tri(tert-butyl)phosphine
	PBS	-	phosphate buffered saline
	Pd/C	-	palladium on carbon
	Pd(PPh ₃) ₄	-	palladium(0)triphenylphosphine
30			tetrakis
	PdCl ₂ (PPh ₃) ₂	-	palladiumdichloro-diphenylphosphine
	Pd(OAc) ₂	-	palladium acetate

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PyBop	-	benzotriazol-1-yl-oxy-tripyrrolidino-phosphonium hexafluorophosphate
RT	-	room temperature
TBTU	-	O-benzotriazol-1-yl-N,N,N',N'-tetramethyluronium tetrafluoroborate
5		
TEA, Et ₃ N	-	triethylamine
TFA	-	trifluoroacetic acid
THF	-	tetrahydrofuran

10

Scheme 1

15 A heteroaryl-substituted alkynes **5** can be prepared according to the method generally described in Scheme 1, wherein the heteroaryl is designated as C, while A and B are independent ring systems, respectively, and "L" is a linker connecting ring A to ring B. As shown, a halogen-substituted

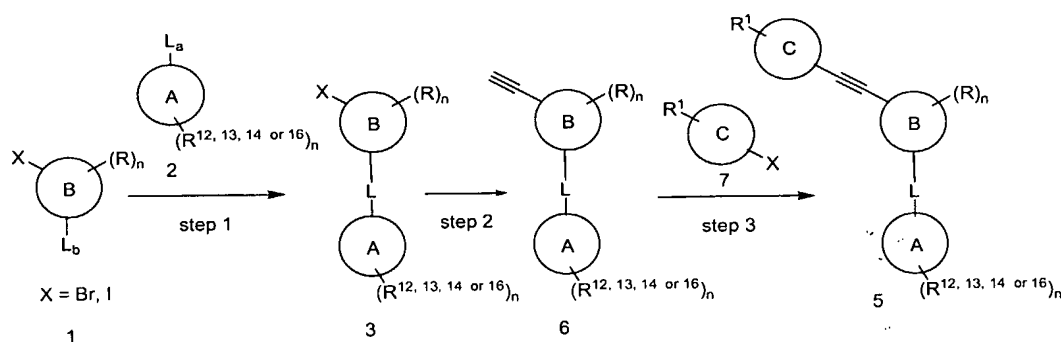
20 B ring system **1**, having a linker portion L_b can be reacted with a substituted A ring system **2** having a corresponding linker portion L_a. Linker portions L_a and L_b are capable of reacting with one another to form compound **3** having the desired linker "L". "L" may be any linker generally defined

25 by the R² substitutions in Formulas I, II and III, and particularly, it includes, without limitation, an amide, a urea, a thiourea, a thioamide, a carbamate, an anhydride, a sulfonamide and the like, allowing for spacer atoms either

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between ring B and L and/or between ring A and L, as described in Scheme 3 below. Accordingly, various desirable linker "L"s can be formed from suitable linker portions L_a and L_b , respectively.

- 5 Halogen-B-A intermediates **3** can be coupled to suitable heteroaryl-substituted alkynes **4** using conventional metallation chemistry methods, such as those disclosed by Stephen Buchwald. For example, compound **3** where X = iodide can be coupled to an alkyne **4** in the presence of palladium and copper under suitable basic solution conditions.
- 10 Generally, suitable palladium reagents include $\text{PdCl}_2(\text{PPh}_3)_2$, and the like. Suitable solvents include polar solvents such as ACN or DMF and suitable bases include weak tertiary amine bases such as TEA. Suitable reaction conditions may involve
- 15 heating the reaction to a suitable temperature to allow complete coupling between the halogen-intermediate **3** and alkyne **4**.

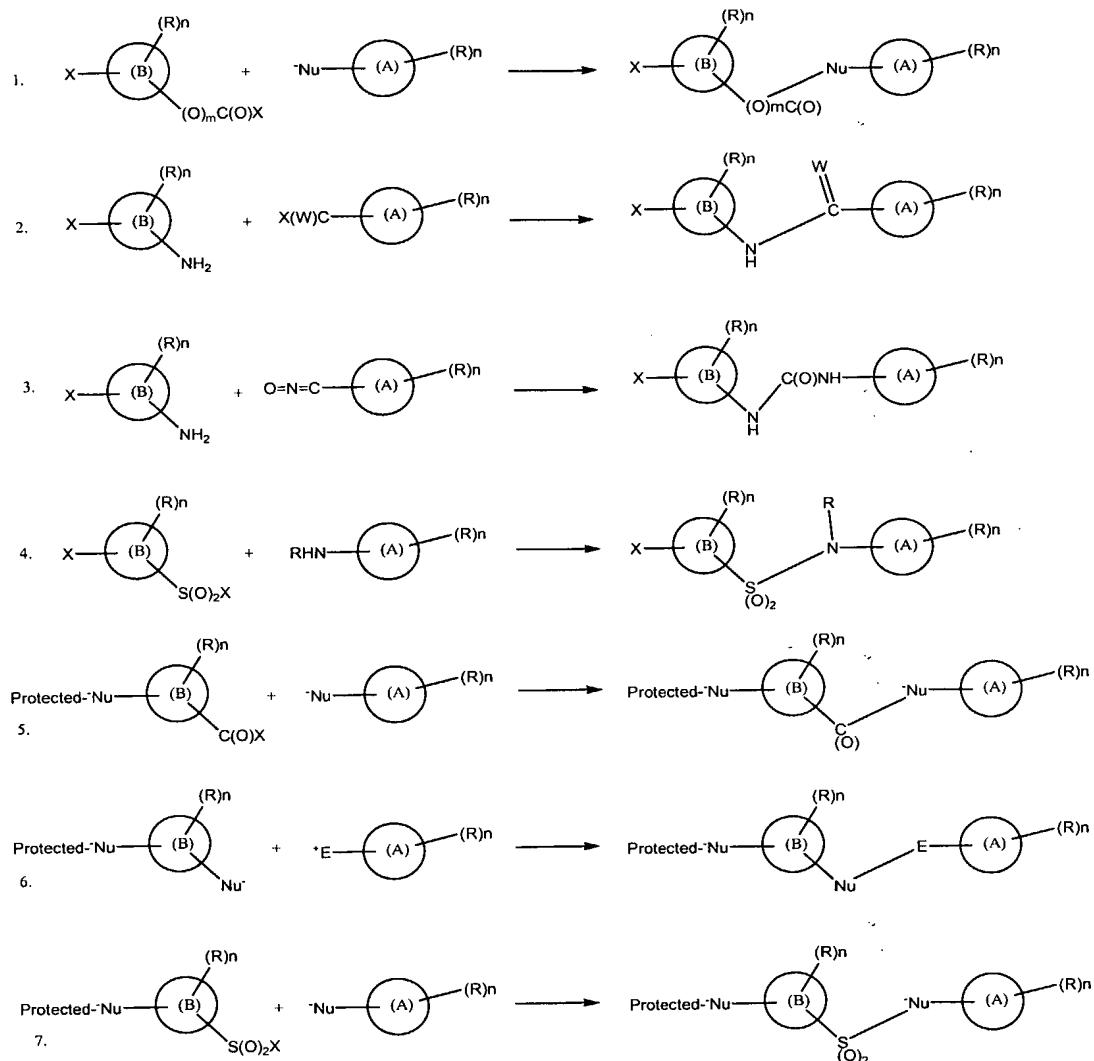
Scheme 2

- Alternatively, heteroaryl-substituted alkynes **5** can be prepared according to the method generally described in
- 25 Scheme 2. As shown and described in scheme 1, a halogen-substituted B ring system-linked-A ring system intermediate **3** can be made. The halogen group of compound **3** can be converted to the corresponding acetylide **6**, as shown in step

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2, by reaction with a suitable acetylene donor, such as a silyl acetylide, under suitable reactions conditions. Such reactions generally take place with suitable metal catalysts, such as palladium and copper. The reaction may
5 proceed under ambient temperature, or may require heat, depending upon the particular intermediate **3**, acetylene reagent, concentration of reagents, solvent, and other factors, as appreciated by persons of ordinary skill in the art.

10 The acetylide **6** can then be reacted with a desired heteroaryl halide **7** to yield the desired heteroaryl-substituted alkyne **5**.

Scheme 3

5 R^2 ring systems, generally designated and referred to in Scheme 3, and throughout the specification, as the "B" ring may be substituted with various substitutions including R^{11} ring systems, generally designated and referred to in Scheme 3, and throughout the specification, as the "A" ring system, by various coupling methods as described in

10 Scheme 3. Each of the seven sub-schemes, numbered 1-7 above and described below, utilize the following meanings for

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(R)_n, X, Nu⁻, E⁺, W and m: (R)_n refers to n number of R¹⁰, R¹¹ and R¹⁶ substitutions wherein n is an integer from 0-9; X refers generally to a "leaving group" such as a halide (bromine, chlorine, iodine or fluorine), alkylsulfonate and other known groups (also see definitions herein); Nu⁻ refers generally to a nucleophilic species such as a primary or secondary amine, an oxygen, a sulfur or a anionic carbon species - examples of nucleophiles include, without limitation, amines, hydroxides, alkoxides and the like; E⁺ refers generally to an electrophilic species, such as the carbon atom of a carbonyl, which is susceptible to nucleophilic attack or readily eliminates - examples of suitable electrophilic carbonyl species include, without limitation, acid halides, mixed anhydrides, aldehydes, carbamoyl-chlorides, sulfonyl chlorides, acids activated with activating reagents such as TBTU, HBTU, HATU, HOBT, BOP, PyBOP, carbodiimides (DCC, EDC and the like), pentafluorophenyl, and other electrophilic species including halides, isocyanates, diazonium ions and the like; W is either O or S; and m is either 0 or 1.

The coupling of rings B and A, as shown as products in sub-schemes 1-7, can be brought about using various conventional methods to link rings B and A together. For example, an amide or a sulfonamide linkage, as shown in sub-schemes 2 and 4, and 5 and 7 where the Nu⁻ is an amine, respectively, can be made utilizing an amine on either the B or A rings and an acid chloride or sulfonyl chloride on the other of either the B or A rings. The reaction proceeds generally in the presence of a suitable solvent and/or base. Suitable solvents include, without limitation, generally non-nucleophilic, a solvent such as toluene, CH₂Cl₂, THF, DMF, DMSO, N,N-dimethylacetamide and the like, including solvent combinations thereof. The solvent may range in polarity, as appreciated by those skilled in the art.

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Suitable bases include, for example, tertiary amine bases such as DIEA, TEA, carbonate bases such as Na_2CO_3 , K_2CO_3 , Cs_2CO_3 , hydrides such as NaH , KH , borohydrides, cyanoborohydrides and the like, alkoxides such as NaOCH_3 ,
5 and the like. The base itself may also serve as a solvent. The reaction may optionally be run neat, i.e., without any base and/or solvent. These coupling reactions are generally fast and conversion occurs typically in ambient conditions. However, depending upon the particular substrate,
10 concentration and other stoichiometric factors, such reactions may require heat, as appreciated by those skilled in the art.

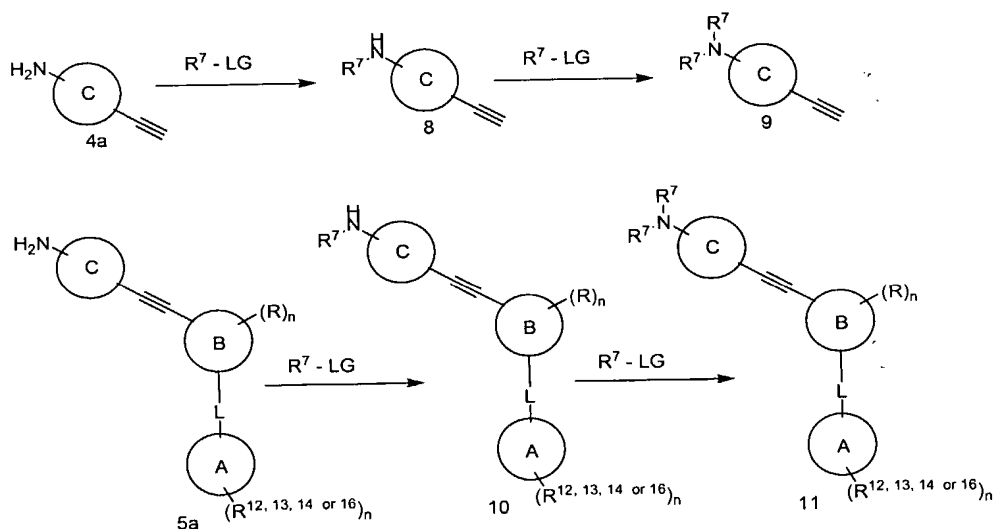
Similarly, carbamates as illustrated in sub-scheme 1 where Nu^- is an amine, anhydrides as illustrated in sub-
15 scheme 1 where Nu^- is an oxygen, reverse amides as generally illustrated in sub-scheme 6 where Nu^- is an amine and E^+ is an acid chloride, ureas as illustrated in sub-scheme 3, thioamides and thioureas where the respective carbonyl oxygen is a sulfur, thiocarbamates where the respective
20 carbonyl oxygen and/or carbamate oxygen is a sulfur, and the like. While the above methods are so described, they are not exhaustive, and other methods for linking rings A and B together may be utilized as appreciated by those skilled in the art.

25 Although sub-schemes 1-7 are illustrated as having the nucleophilic and electrophilic coupling groups, such as the amino group and acid chloride groups illustrated in sub-scheme 2, directly attached to the substrate, either the A or B ring, in question, the invention is not so limited. It
30 is contemplated herein that these nucleophilic and/or electrophilic coupling groups may be tethered from their respective ring. For example, the amine group on the B ring, and/or the acid halide group on the A ring, as illustrated in sub-scheme 2, may be removed from direct attachment to

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the ring by a one or more atom spacer, such as by a methylene, ethylene, propylene spacer or the like. As appreciated by those skilled in the art, such spacer may or may not affect the coupling reactions described above, and accordingly, such reaction conditions may need to be modified to affect the desired transformation.

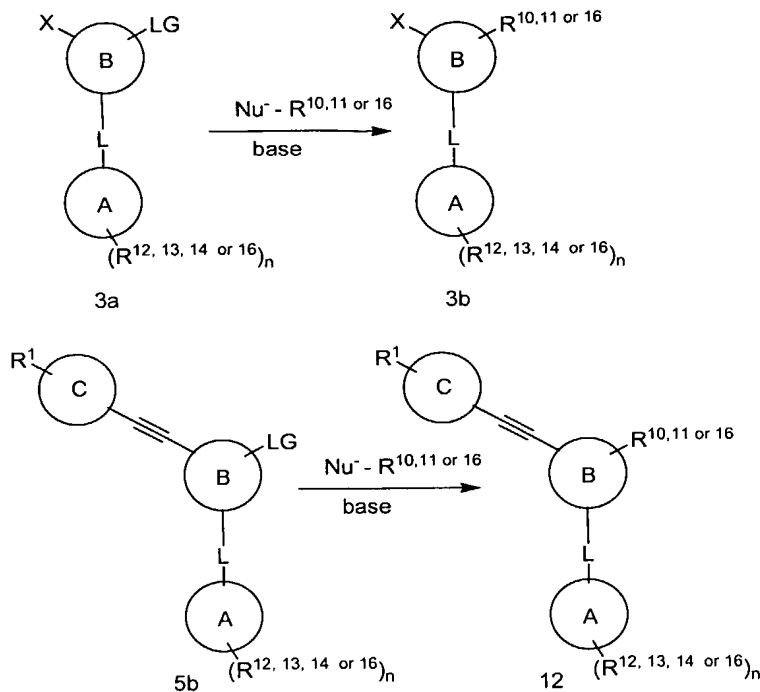
The coupling methods described in sub-schemes 1-7 of scheme 3 are also applicable for coupling desired A rings to desired C-B intermediates, to synthesize desired compounds of Formulas I, II and III. For example, a halo-B-NH₂ ring may first be coupled to a heteroaryl-substituted alkynyl intermediate 4 (scheme 1, also referred to as the C ring) to form the C-B intermediate. The B ring amine group of this C-B intermediate may then be converted to an isocyanate, for example, or any other desired group for coupling the A ring via the desired linker. Further, the B ring amine may be protected, such as with BOC-ON, while further substituents are coupled to the B ring and/or the C ring, prior to coupling the C-B intermediate to an A ring (see Scheme 5 below).

Scheme 4

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Various R⁷ substitutions and/or R⁸ substitutions (not shown) can be installed in the C ring portion, at a desired location on the C ring of the compounds of Formulas I, II and III, with or without the B-A ring system attached, as described in Scheme 4. For instance, compounds **8**, **9**, **10** and **11** may be made by the method described in Scheme 4. As shown, amino substitutions R⁷ may be made by reacting the amino heteroaryl substituted alkyne compound **4a** with a desired R group having a leaving group ("LG"), suitable for reaction with an aryl NH₂. For example, a methyl group may be covalently bound to the amine via reaction with methyl iodide. Similarly, a 2-dimethylamino substitution may be obtained via excess methyl iodide, or similar methylating reagent. Base may or may not be needed, as appreciated by those skilled in the art. Similarly, amide or sulfonamide linkers may be obtained where R⁷ (or R⁸) is an activated carbonyl or sulfonyl species, such as an acid or sulfonyl chloride and the like. The acetylene group on compound **4a** may need to be protected such as with a silyl group or the like, to prevent reaction at that site during the reaction to install the R⁷ and/or R⁸ groups, and later deprotected to couple the desired C ring system to the desired B-A ring system, utilizing methods described in Scheme 3. Such is readily appreciated by those skilled in the art. Such protection may or may not be necessary while functionalizing an amino group off of the C ring in compound **10**, depending upon the particular substitutions on rings A and B.

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Scheme 5

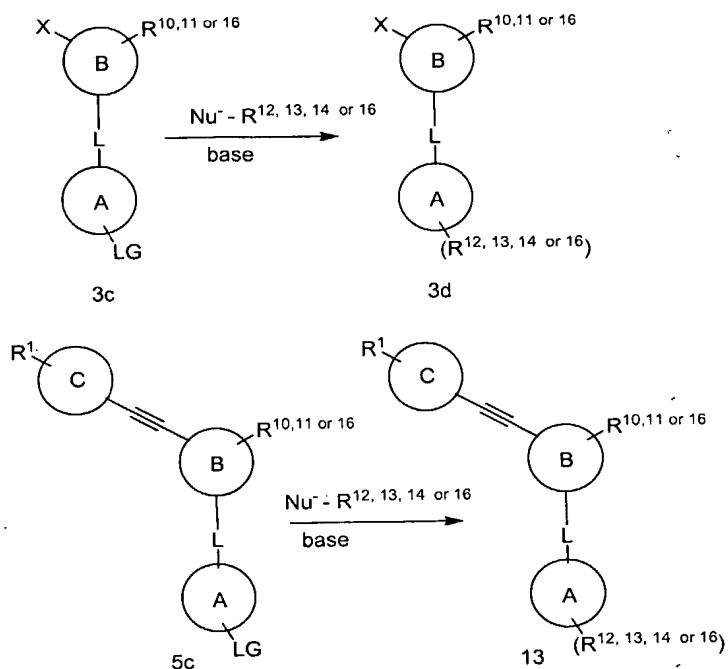
- 5 Various R^{10} , R^{11} and R^{16} substitutions, as shown on compounds **3b** and **12**, can be installed on the B ring of Formulas I - III, with or without the C ring system attached, as described in Scheme 5. For instance, compounds **3b** and **12** may be made by the method described in Scheme 5.
- 10 As shown, iodinated compounds **3a** ($X = I$) and compounds **5b** may contain suitable leaving groups, such as a fluoride, at a desired position on the B ring for substitution. Intermediates **3a** and **5b** may be reacted with desirable nucleophilic R groups (R^{10} , R^{11} and R^{16} substitutions), such
- 15 as alkoxides, amines and the like, in the presence of a suitable base, such as a hydride or borohydride, to covalently bind the R group to the B ring. Alternatively, the B ring may have a nucleophile (not shown), such as a hydroxide or an amine, which may be further functionalized

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as desired via standard chemical methodology, as appreciated by those skilled in the art.

Scheme 6

5



Various R^{12} , R^{13} , R^{14} and R^{16} substitutions, as shown on compounds **3d** and **13**, can be installed on the A ring of Formulas I - III, with or without the C ring system attached, as described in Scheme 6. For instance, compounds **3d** and **13** may be made by the method described in Scheme 6. As shown, iodinated ($X = I$; or amino-protected, which is not shown) aryl B ring compounds **3c**, and compounds **5c** may contain suitable leaving groups on the A ring, such as a halide, sulfonate, activated acid, anhydride, ester, hydroxide and the like, at a desired position for substitution. Intermediates **3c** and **5c** may be reacted with desirable nucleophilic R groups (R^{12} , R^{13} , R^{14} and R^{16} substitutions), such as alkoxides, amines and the like, in the presence of a suitable base, such as a tertiary amine

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base, carbonate or bicarbonate bases, hydride or borohydride bases, hydroxide and alkoxide bases, and stronger bases as necessary, to covalently bind the R group to the A ring. Other R groups such as aryl rings, acetylene groups, and the like may be attached utilizing Suzuki methods or other metal chemistry as appreciated by the skilled artisan. Alternatively, the A ring may have a nucleophile, such as a hydroxide or an amine, which may be further functionalized as desired via standard chemical methodology, as appreciated by those skilled in the art.

To enhance the understanding and appreciation of the present invention, the following exemplary methods and specific examples (starting reagents, intermediates and compounds of Formulas I, II and III) are set forth. It should be appreciated that these methods and examples are merely for illustrative purposes only and are not to be construed as limiting the scope of this invention in any manner.

Analytical methods:

Unless otherwise indicated, all HPLC analyses were run on a Agilent Model 1100 system with an Agilent Technologies Zorbax SB-C₈(5 μ) reverse phase column (4.6 x 150 mm; Part no. 883975-906) run at 30 °C with a flow rate of about 1.50 mL/min. The mobile phase used solvent A (H₂O/0.1% TFA) and solvent B (ACN/0.1% TFA) with a 11 min gradient from 5% to 100% ACN. The gradient was followed by a 2 min. return to 5% ACN and about a 2.5 min. re-equilibration (flush).

LC-MS Method:

Samples were run on an Agilent model-1100 LC-MSD system with an Agilent Technologies XDB-C₈ (3.5 μ) reverse phase column (4.6 x 75 mm) at 30 °C. The flow rate was

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constant and ranged from about 0.75 mL/min to about 1.0 mL/min.

The mobile phase used a mixture of solvent A (H₂O/0.1% HOAc) and solvent B (ACN/0.1% HOAc) with a 9 min time period for a gradient from 10% to 90% solvent B. The gradient was followed by a 0.5 min period to return to 10% solvent B and a 2.5 min 10% solvent B re-equilibration (flush) of the column.

10 **Preparative HPLC Method:**

Where indicated, compounds of interest were purified via reverse phase HPLC using a Gilson workstation utilizing one of the following two columns and methods:

(A) Using a 50 x 100 mm column (Waters, Exterra, C18, 5 microns) at 50 mL/min. The mobile phase used was a mixture of solvent A (H₂O/10 mM ammonium carbonate at pH about 10, adjusted with conc. NH₄OH) and solvent B (85:15 ACN/water, 10 mM ammonium carbonate at pH of about 10 adjusted with conc. NH₄OH). Each purification run utilized a 10 minute gradient from 40% to 100% solvent B followed by a 5 minute flow of 100% solvent B. The gradient was followed by a 2 min return to 40% solvent B.

(B) Using a 20 x 50 mm column at 20 mL/min. The mobile phase used was a mixture of solvent A (H₂O/0.1% TFA) and solvent B (ACN/0.1% TFA) with a 10 min gradient from 5% to 100% solvent B. The gradient is followed by a 2 min return to 5% ACN.

Proton NMR Spectra:

30 Unless otherwise indicated, all ¹H NMR spectra were run on a Varian series Mercury 300 MHz instrument or a Bruker series 400MHz instrument. Where so characterized, all observed protons are reported as parts-per-million (ppm)

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downfield from tetramethylsilane (TMS) or other internal reference in the appropriate solvent indicated.

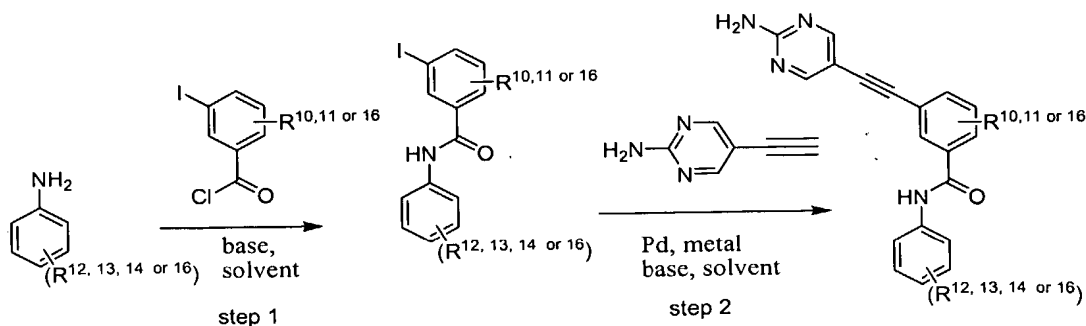
Mass Spectra (MS)

5 Unless otherwise indicated, all mass spectral data for starting materials, intermediates and/or exemplary compounds are reported as mass/charge (m/z), having an ($M+H^+$) molecular ion. The molecular ion reported was obtained by electrospray detection method. Compounds having an isotopic
10 atom, such as bromine and the like, are reported according to the detected isotopic pattern, as appreciated by those skilled in the art.

The following examples represent various starting materials and intermediates, which should assist in better
15 understanding and appreciating the exemplary methods of synthesizing compounds of Formulas I, II and III.

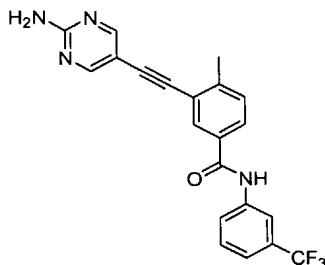
Various experimental methods have been employed to synthesize compounds of Formulas I - III, as more generally
described in schemes 1-6 above, and further described in
20 more detail by the representative examples below.

Experimental Method A1



25

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Example 1**Synthesis of 3-(2-(2-aminopyrimidin-5-yl)ethynyl)-4-methyl-N-(3-(trifluoromethyl)phenyl)benzamide.**Step 1. Preparation of 3-iodo-4-methyl-N-(3-(trifluoromethyl)phenyl)benzamide

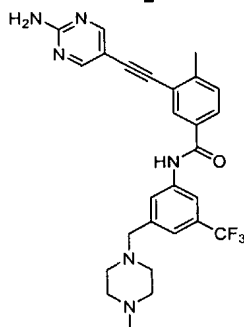
3-Iodo-4-methylbenzoic acid (2.0 g, 7.6 mmol) was taken up in SOCl_2 (4 mL). The resulting slurry was allowed to reflux for 2h upon which time the reaction was concentrated under reduced pressure to afford the corresponding acid chloride, which was used without further purification. The off white acid-chloride solid was taken up in CH_2Cl_2 (70 mL) followed by the addition of DIEA (1.5 mL, 8.4 mmol) and 3-(trifluoromethyl)aniline (0.86 mL, 6.9 mmol). The mixture was allowed to stir at room temperature for 3 h. The reaction mixture was diluted with CH_2Cl_2 (70 mL) and washed with aq. HCl (1M, 25 mL), sat. aq. NaHCO_3 (25 mL), brine (25 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford 3-iodo-4-methyl-N-(3-(trifluoromethyl)phenyl)benzamide as an off white solid. MS m/z = 406 $[\text{M}+\text{H}]^+$. Calc'd for $\text{C}_{15}\text{H}_{11}\text{F}_3\text{INO}$: 405

Step 2: Preparation of 3-(2-(2-aminopyrimidin-5-yl)ethynyl)-4-methyl-N-(3-(trifluoromethyl)phenyl)benzamide

To a sealable tube containing 5-ethynylpyrimidin-2-amine (172 mg, 1.44 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (25 mg, 0.036 mmol), 3-iodo-4-methyl-N-(3-(trifluoromethyl)phenyl)benzamide (292 mg, 0.72 mmol) was added MeCN (10 mL) and Et_3N (3 mL) followed by CuI (6.8 mg, 0.036 mmol). The tube was sealed

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and heated at 90° C for 1 h. The reaction was allowed to cool to room temperature and concentrated under reduced pressure. The resulting brown solid was reconstituted in MeOH:CH₂Cl₂ (1:1, 10 mL) and silica gel was added and
 5 reconcentrated. The silica-gel combined crude mixture was purified via automated flash chromatography (silica gel, 0 to 5% MeOH in CH₂Cl₂, gradient elution) to afford 3-(2-(2-aminopyrimidin-5-yl)ethynyl)-4-methyl-N-(3-(trifluoromethyl)phenyl)benzamide. MS *m/z* = 397 [M+H]⁺.
 10 Calc'd for C₂₁H₁₅F₃N₄O: 396

Example 2

Synthesis of 3-(2-(2-aminopyrimidin-5-yl)ethynyl)-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)benzamide:
 15

Step 1: Preparation of 3-iodo-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)benzamide
 20

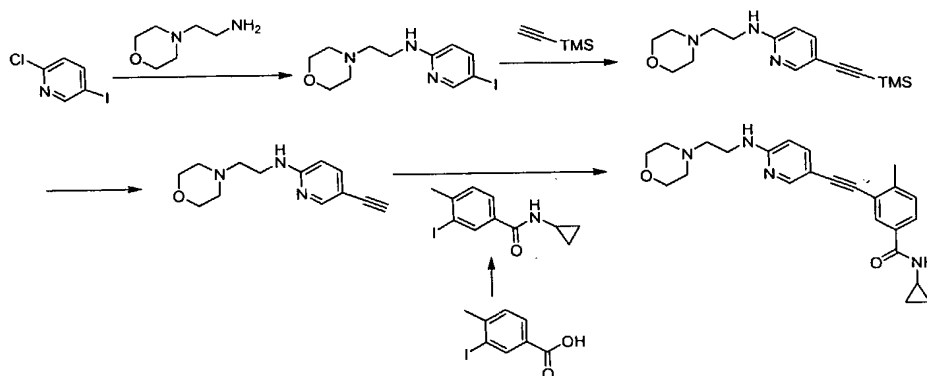
To a solution of 3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)-benzenamine (0.274g , 1 mmol) in CH₂Cl₂ (3 mL) at room temperature was added 3-iodo-4-methylbenzoyl chloride (0.267 g, 0.95 mmol). The mixture was allowed to stir for 20 h. The reaction was concentrated under reduced
 25 pressure, and purified via column chromatography (0 to 20% methanol in dichloromethane) to afford 3-iodo-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)benzamide. MS *m/z* = 518. Calc'd for
 30 C₂₄H₁₈ClF₃N₄O: 517.33.

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Step 2: Preparation of 3-(2-(2-aminopyrimidin-5-yl)ethynyl)-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)benzamide

5 Aryl iodide (0.113 g, 0.22 mmol), 2-amino-5-ethynylpyrimidine (0.53g, 0.44 mmol), Palladium dichloro-bis-triphenylphosphine (0.008 g, 0.011 mmol), and copper(I) iodide were placed into a vial. Acetonitrile (10mL) and triethylamine (2mL) were added, and the mixture was heated
 10 with stirring at 90C for 1 hour. The mixture was cooled to room temperature, concentrated under reduced pressure and adsorbed onto silica gel. Flash chromatography of the pre-absorbed mixture (eluting with 0 to 20% methanol in dichloromethane) afforded 3-(2-(2-aminopyrimidin-5-yl)ethynyl)-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)benzamide as a yellow semi-solid.
 15 MS m/z = 509. Calc'd for $C_{24}H_{18}ClF_3N_4O$: 508.54.

Example 2a



20

Synthesis of N-cyclopropyl-4-methyl-3-(2-(6-(2-morpholinoethylamino)pyridin-3-yl)ethynyl)benzamide

Step 1: 5-iodo-N-(2-morpholinoethyl)pyridin-2-amine

25 2-Chloro-5-iodopyridine (2.21 g, 9.25 mmol) was dissolved in 2-morpholinoethanamine (10 mL) and placed in the microwave for 30 min. at about 180°C. The reaction mixture was diluted with 100 mL EtOAc, washed with 50 mL saturated, aqueous $NaHCO_3$, and dried over anhydrous Na_2SO_4 . After

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purification by chromatography, the title compound was obtained. MS (ES+): 334 (M+H)⁺.

Step 2: N-(2-morpholinoethyl)-5-(2-(trimethylsilyl)ethynyl)pyridin-2-amine

5 5-Iodo-N-(2-morpholinoethyl)pyridin-2-amine (0.82 g, 2.46 mmol), TMS acetylene (1.70 mL, 12.3 mmol), and triethylamine (0.69 mL, 4.92 mmol) were dissolved in dioxane (20 mL) and with nitrogen for about 15 min.

10 Tetrakis(triphenylphosphine)palladium (142 mg, 0.12 mmol) and copper (I) iodide (47 mg, 0.25 mmol) were added before the reaction mixture was heated to 80°C for 3.5 h. The reaction mixture was diluted with 100 mL EtOAc, washed with 50 mL saturated, aqueous NaHCO₃, and dried over anhydrous
15 Na₂SO₄. After purification by chromatography, the title compound was obtained. MS (ES+): 304 (M+H)⁺.

Step 3: 5-ethynyl-N-(2-morpholinoethyl)pyridin-2-amine

N-(2-morpholinoethyl)-5-(2-(trimethylsilyl)ethynyl)pyridin-2-amine (2.0 g, 6.60 mmol) was dissolved in methanol (30 mL)
20 before it was cooled to 0°C and potassium carbonate (1.0 g, 7.26 mmol) added. The reaction mixture was stirred for 1 h at ambient temperature, then diluted with 50 mL EtOAc, washed with 20 mL saturated, aqueous NaHCO₃, and dried over anhydrous Na₂SO₄ to give the title compound. MS (ES+): 232
25 (M+H)⁺.

Step 4: N-cyclopropyl-3-iodo-4-methylbenzamide

To 3-iodo-4-methylbenzoic acid (3.5 g, 13 mmol) was added thionyl chloride (10 mL) before heating the mixture to reflux for 1.5 h. The reaction mixture was concentrated in
30 vacuo, and dissolved in DCM (50 mL) and Hünigs base (4.6 mL, 27 mmol). After the addition of cyclopropylamine (1.87 mL, 27 mmol) at -78 °C, the reaction mixture was stirred at ambient Temp. for about 3 h. The mixture was diluted with 100 mL DCM, washed with 20 mL saturated, aqueous NaHCO₃ and
35 20 mL 3 N HCl, and dried over anhydrous Na₂SO₄. The solid

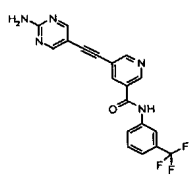
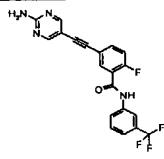
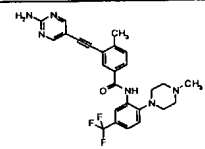
- 96 -

obtained was suspended in EtOAc and filtered to give the title compound. MS (ES⁺): 302 (M+H)⁺.

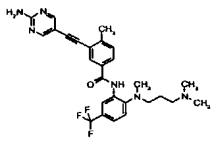
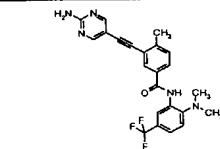
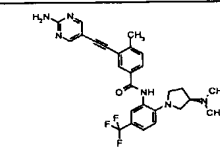
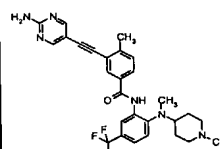
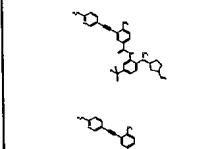
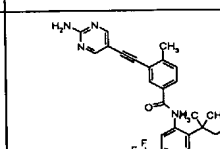
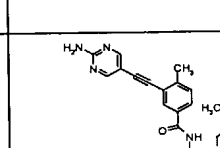
Step 5: N-cyclopropyl-4-methyl-3-(2-(6-(2-morpholinoethylamino)pyridin-3-yl)ethynyl)benzamide

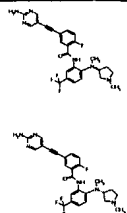
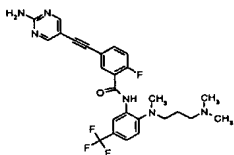
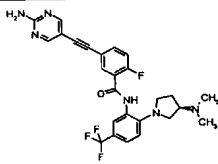
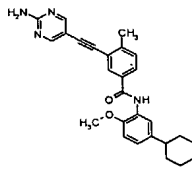
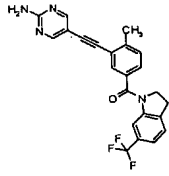
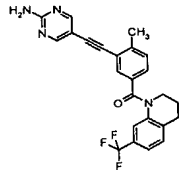
- 5 5-Ethynyl-N-(2-morpholinoethyl)pyridin-2-amine (0.54 g, 2.36 mmol), N-cyclopropyl-3-iodo-4-methylbenzamide (0.71 g, 2.36 mmol), and triethylamine (0.49 mL, 3.54 mmol) were dissolved in dioxane (10 mL) before these were sparged with nitrogen
- 10 for 15 min.; palladium dichloro-bis-triphenylphosphine (83 mg, 0.12 mmol) and copper (I) iodide (45 mg, 0.24 mmol) were added before the reaction mixture was heated to 90 °C for 6 h. The reaction mixture was diluted with 100 mL EtOAc, washed with 50 mL saturated, aqueous NaHCO₃, and dried over
- 15 anhydrous Na₂SO₄. After purification by chromatography, the title compound was obtained as a yellow oil. MS (ES⁺): 406 (M+H)⁺.

- The following Examples 3-75 were prepared by a method similar to that described in Experimental Method A1 and
- 20 Examples 1, 2 and 2a.

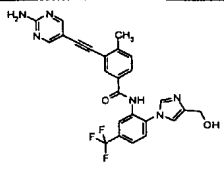
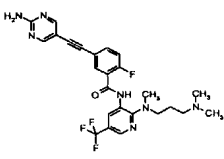
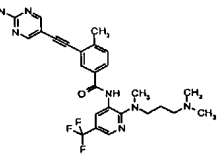
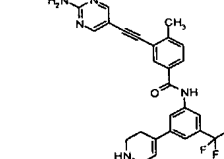
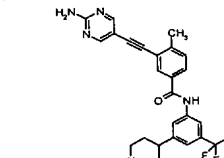
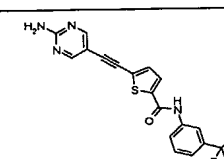
Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
3		A1	383.33	384	
4		A1	400.33	401	
5		A1	494.52	495	

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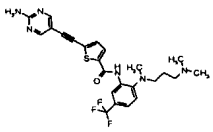
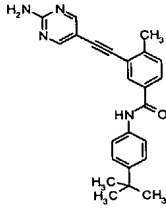
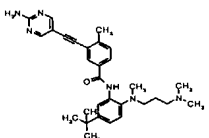
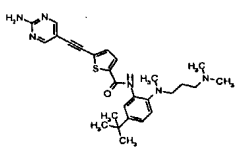
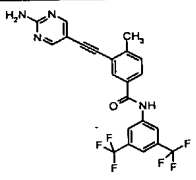
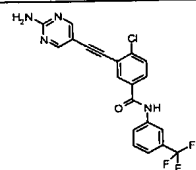
Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
6		A1	510.56	511	
7		A1	439.44	440	
8		A1	508.55	509	
9		A1	522.57	523	
10		A1	508.5	509	
11		A1	495.55	496	
12		A1	522.57	523	

Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
13		A1	512.5	513	
14		A1	514.52	515	
15		A1	512.51	513	
16		A1	440.54	441	
17		A1	422.41	423	
18		A1	436.44	437	

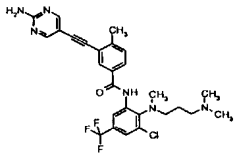
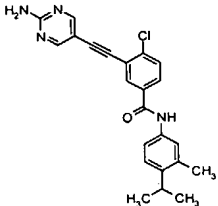
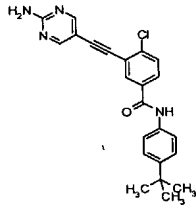
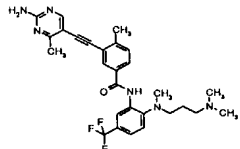
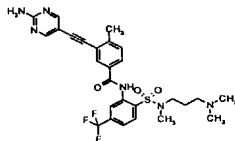
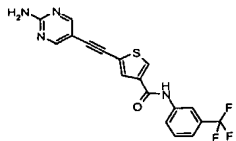
- 99 -

Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
19		A1	492.46	493	
20		A1	515.51	516	
21		A1	511.55	512	
22		A1	477.49	478	
23		A1	493.53	494	
24		A1	388.37	389	

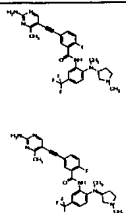
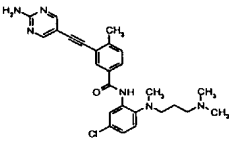
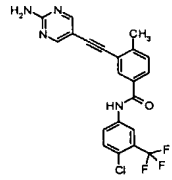
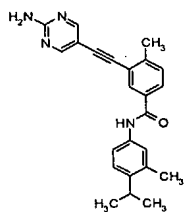
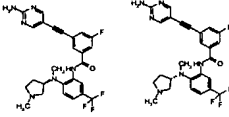
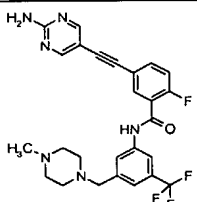
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Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
25		A1	502.56	503	
26		A1	384.48	385	
27		A1	498.67	500	
28		A1	490.67	491	
29		A1	464.37	465	
30		A1	416.79	417	

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Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
31		A1	545.01	545	
32		A1	404.9	405	
33		A1	404.9	405	
34		A1	524.59	525	
35		A1	574.63	575	
36		A1	388.37	389	

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Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
37		A1	526.5	527	
38		A1	477.01	477	
39		A1	430.82		429
40		A1	384.48		383
41		A1	512.5	513	
42		A1	512.51	513	

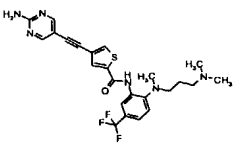
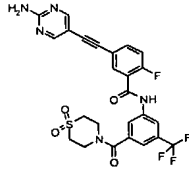
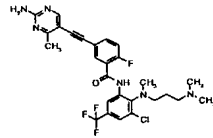
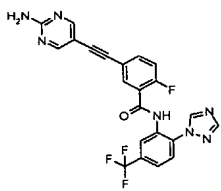
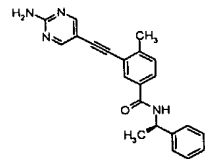
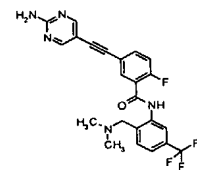
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Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
43		A1	522.53	523	
44		A1	526.49	527	
45		A1	426.4		425
46		A1	558.58	559	
47		A1	485.53	486	
48		A1	548.97	549	

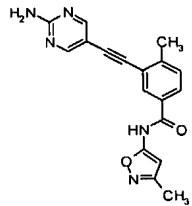
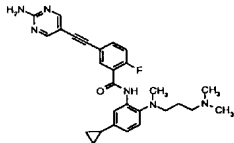
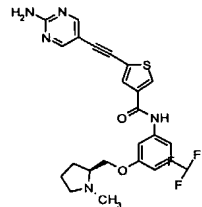
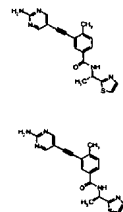
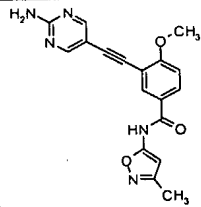
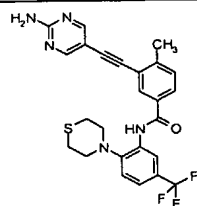
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Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
49		A1	578.59	579	
50		A1	562.55	563	
51		A1	410.4		409
52		A1	412.37		411
53			428.37		427
54		A1	502.56	503	

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Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
55		A1	502.56	503	
56		A1	561.51	562	
57		A1	563	563	
58		A1	467.38	468	
59		A1	356.43	357	
60		A1	457.43	458	

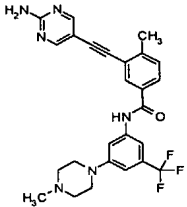
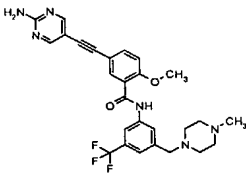
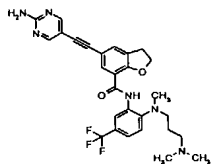
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Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
61		A1	333.35		332
62		A1	486.59	487	
63		A1	501.53	502	
64		A1	363.4	364	
65		A1	349.35		348
66		A1	497.54	498	

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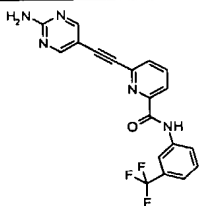
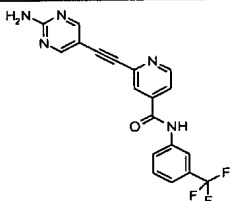
Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
67		A1	347.38		346
68		A1	363.38		362
69		A1	509.53		508
70		A1	430.43	431	
71		A1	512.51	513	
72		A1	512.51	513	

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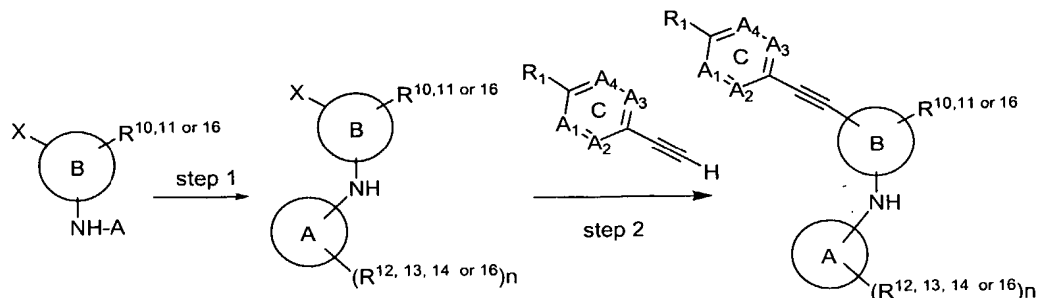
Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
73		A1	494.52		493
74		A1	524.54	525	
75		A1	538.57	539	

The following Examples 76-77 were prepared by a method (Method A2) similar to that described in Experimental Method A1 and Example 2, utilizing a conventional acid to amine

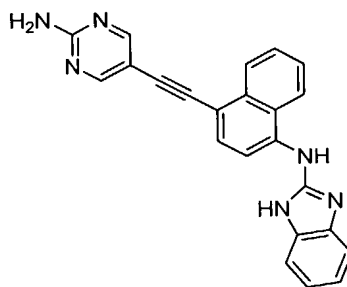
5 coupling reagent, such as HOBT, HATU, HBTU, pentafluorophenyl ester and the like, in step 1.

Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
76		A1	383.33	384	
77		A1	383.33	384	

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Experimental Method A3

5

Example 77-V

10 **N-(4-(2-(2-aminopyrimidin-5-yl)ethynyl)naphthalen-1-yl)-1H-benzo[d]imidazol-2-amine**

Step 1: 1-bromo-4-isothiocyanatonaphthalene

To a solution of 1-bromo-4-aminonaphthalene (2.6 g, 12 mmol) in dichloromethane (45 mL) was added di(1H-imidazol-1-yl)methanethione (2.1 g, 12 mmol). The reaction was allowed to stir for 16 h, at which point the reaction was concentrated to give a gray solid. The solid was slurried in 50% EtOAc/hexanes and filtered through a pad of silica gel, rinsing with 400 mL 50% EtOAc/hexanes. The solution was concentrated to give 1-bromo-4-isothiocyanatonaphthalene as a gray solid, which was used without further purification.

20 Step 2: N-(4-bromonaphthalen-1-yl)-1H-benzo[d]imidazol-2-amine

25

A slurry of 1-bromo-4-isothiocyanatonaphthalene (1.0 g, 3.8 mmol), o-phenylene diamine (0.45 g, 4.2 mmol), and polymer-

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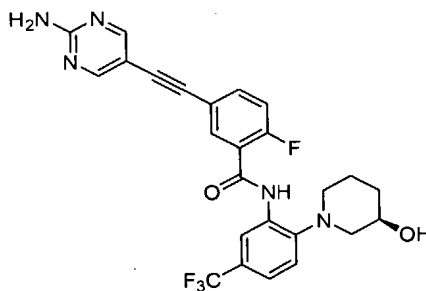
supported carbodiimide (9.0 g, 11 mmol, 1.27 mmol/g) in 72 mL THF was heated to 70°C with a water-cooled reflux condenser for 3 h. The reaction was filtered, rinsing with dichloromethane. The solution was concentrated to a yellow solid, suspended in dichloromethane, and filtered, rinsing with a small quantity of diethyl ether to give N-(4-bromonaphthalen-1-yl)-1H-benzo[d]imidazol-2-amine as a white solid. MS m/z = 338 $[M+1]^+$. Calc'd for $C_{17}H_{12}BrN_3$: 337

10 Step 3 N-(4-(2-(2-aminopyrimidin-5-yl)ethynyl)naphthalen-1-yl)-1H-benzo[d]imidazol-2-amine

The title compound was prepared in a manner to that described in experimental procedure A1 step 2. MS m/z = 377 $[M+1]^+$. Calc'd for $C_{23}H_{16}N_6$: 376

15

Example 77-V-1



20 **Synthesis of (R)-5-(2-(2-aminopyrimidin-5-yl)ethynyl)-2-fluoro-N-(2-(3-hydroxypiperidin-1-yl)-5-(trifluoromethyl)phenyl)benzamide**

25 Step 1: Preparation of (R)-1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-ol

To a 100-mL round bottom flask (RBF) was added (R)-piperidin-3-ol hydrochloride (1.29 g, 9.37 mmol), sodium bicarbonate (2.76 g, 32.8 mmol), THF and 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (1.31 mL, 9.37 mmol). The yellow mixture was heated to 75°C. with a water-cooled reflux condensor and allowed to stir 14 h. The reaction was

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filtered through a glass frit, rinsing with EtOAc, and concentrated in vacuo to give (R)-1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-ol as an orange oil.

5 Step 2: Preparation of (R)-3-(tert-butyldimethylsilyloxy)-1-(2-nitro-4-(trifluoromethyl)phenyl)piperidine

To a solution of (R)-1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-ol (3.35 g, 11.5 mmol) and imidazole (1.02 g, 15.0 mmol) in DMF at ambient
10 temperature under nitrogen was added tert-butyldimethylsilylchloride (1.91 g, 12.7 mmol). The reaction was allowed to stir for 24 h, at which point additional 0.3 g tert-butyldimethylsilylchloride was added. The reaction was allowed to stir for an additional 14 h, and
15 was then poured into Et₂O/saturated aqueous NaHCO₃. The organic layer was washed 2x H₂O, 1x brine, dried over anhydrous MgSO₄, filtered and concentrated to a yellow oil. The crude material was treated with hexanes and adsorbed onto silica gel and passed through a Redi-Sep® pre-packed
20 silica gel column (80 g) eluting with 0 - 20% EtOAc/hexane. The product-containing fractions were concentrated to afford (R)-3-(tert-butyldimethylsilyloxy)-1-(2-nitro-4-(trifluoromethyl)phenyl)piperidine as a yellow oil. MS m/z = 405 [M+H]⁺. Calc'd for C₁₈H₂₇F₃N₂O₃Si: 404.

25 Step 3: Preparation of (R)-2-(3-(tert-butyldimethylsilyloxy)piperidin-1-yl)-5-(trifluoromethyl)benzenamine

A 200 mL RBF was charged with (R)-3-(tert-butyldimethylsilyloxy)-1-(2-nitro-4-(trifluoromethyl)phenyl)piperidine (4.10 g, 10.1 mmol) and
30 palladium, 10 wt.% on activated carbon wet (0.179 ml, 2.03 mmol) under nitrogen. MeOH was added via syringe, and the atmosphere replaced with hydrogen via one or more balloons. The reaction was stirred rapidly for 60 h. The reaction was
35 flushed with nitrogen, filtered through celite rinsing with

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100 mL MeOH, and concentrated in vacuo. The crude material was treated with hexanes and passed through a Redi-Sep® pre-packed silica gel column (80 g) eluting with 0 - 40% EtOAc/hexane. The product-containing fractions were

5 concentrated to afford (R)-2-(3-(tert-butyl dimethylsilyloxy)piperidin-1-yl)-5-(trifluoromethyl)benzenamine as a brown oil. MS m/z = 375 $[M+H]^+$. Calc'd for $C_{18}H_{29}F_3N_2OSi$: 374.

10 Step 4: Preparation of (R)-N-(2-(3-(tert-butyl dimethylsilyloxy)piperidin-1-yl)-5-(trifluoromethyl)phenyl)-2-fluoro-5-iodobenzamide

In a vial, (R)-2-(3-(tert-butyl dimethylsilyloxy)piperidin-1-yl)-5-(trifluoromethyl)benzenamine (.517 g, 1.4 mmol) was
15 taken up in THF. Triethylamine (0.29 mL, 2.1 mmol) and 2-fluoro-5-iodobenzoyl chloride (0.43 g, 1.5 mmol) were added. The vial was sealed and the reaction stirred for 48 h. The reaction mixture was poured into EtOAc/1N NaOH. The organic layer was dried over anhydrous sodium sulfate and
20 concentrated in vacuo. The crude material was treated with hexanes and passed through a Redi-Sep® pre-packed silica gel column (40 g) eluting with 0 - 10% EtOAc/hexane. The product-containing fractions were concentrated to afford
(R)-N-(2-(3-(tert-butyl dimethylsilyloxy)piperidin-1-yl)-5-(trifluoromethyl)phenyl)-2-fluoro-5-iodobenzamide as a white
25 foam.

30 Step 5: Preparation of (R)-5-(2-(2-aminopyrimidin-5-yl)ethynyl)-N-(2-(3-(tert-butyl dimethylsilyloxy)piperidin-1-yl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide

In a 16 x120 mm resealable pyrex tube, 5-ethynylpyrimidin-2-amine (0.080 g, 0.67 mmol), (R)-N-(2-(3-(tert-butyl dimethylsilyloxy)piperidin-1-yl)-5-(trifluoromethyl)phenyl)-2-fluoro-5-iodobenzamide (.210 g,
35 0.34 mmol), Bis(triphenylphosphine)palladium(II) dichloride (0.012 g, 0.017 mmol), and Copper(I) iodide (0.0032 g, 0.017

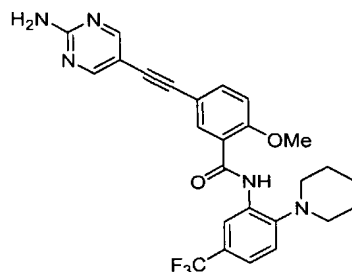
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mmol) were taken up in CH₃CN and Triethylamine (0.71 ml, 5.1 mmol) was added, and the tube was flushed with nitrogen. The tube was sealed and the reaction heated to 70°C overnight. The reaction was cooled, and transferred to a 50 mL RBF with EtOAc. The mixture was concentrated in vacuo, and the resulting solid was treated with 10% MeOH in CH₂Cl₂ and adsorbed onto 1.5 g silica gel and passed through a Redi-Sep® pre-packed silica gel column (40 g) eluting with 0 - 60% EtOAc/hexane. The product-containing fractions were concentrated to afford (R)-5-(2-(2-aminopyrimidin-5-yl)ethynyl)-N-(2-(3-(tert-butyldimethylsilyloxy)piperidin-1-yl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide as an off-white solid.

15 Step 6: Preparation of (R)-5-(2-(2-aminopyrimidin-5-yl)ethynyl)-2-fluoro-N-(2-(3-hydroxypiperidin-1-yl)-5-(trifluoromethyl)phenyl)

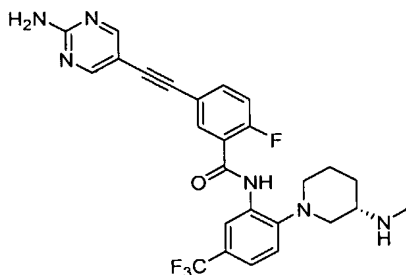
To a yellow solution of (R)-5-(2-(2-aminopyrimidin-5-yl)ethynyl)-N-(2-(3-(tert-butyldimethylsilyloxy)piperidin-1-yl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide (.162 g, 0.264 mmol) was added tetrabutylammonium fluoride, 1.0 M in THF (0.688 ml, 2.38 mmol). The reaction was allowed to stir for 6 h, at which point it was found by TLC analysis to be complete. The reaction was diluted with EtOAc and washed once with brine. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo to give a yellow oil, which was purified by silica gel chromatography, 0-10% MeOH/MC to give (R)-5-(2-(2-aminopyrimidin-5-yl)ethynyl)-2-fluoro-N-(2-(3-hydroxypiperidin-1-yl)-5-(trifluoromethyl)phenyl)benzamide as an off-white solid. MS m/z = 500 [M+H]⁺. Calc'd for C₂₅H₂₁F₄N₅O₂: 499.

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Example 77-V-2**5 Synthesis of 5-(2-(2-aminopyrimidin-5-yl)ethynyl)-2-methoxy-N-(2-(piperidin-1-yl)-5-(trifluoromethyl)phenyl)benzamide**

A mixture of 5-(2-(2-aminopyrimidin-5-yl)ethynyl)-2-fluoro-N-(2-(piperidin-1-yl)-5-(trifluoromethyl)phenyl)benzamide (0.14 g, 0.29 mmol) and NaOMe (0.5 M solution in methanol, 2.0 mL, 1.0 mmol) in a sealed tube was heated to reflux. After 16 h, the reaction was cooled and partitioned between EtOAc and brine. The organic layer was dried over anhydrous sodium sulfate, filtered, and concentrated. The material was purified by preparative TLC, eluting with 30% acetone/dichloromethane to give 5-(2-(2-aminopyrimidin-5-yl)ethynyl)-2-methoxy-N-(2-(piperidin-1-yl)-5-(trifluoromethyl)phenyl)benzamide as a white solid. MS m/z = 496 $[M+H]^+$. Calc'd for $C_{26}H_{24}F_3N_5O_2$: 495.

20

Example 77-V-3

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Synthesis of (S)-5-(2-(2-aminopyrimidin-5-yl)ethynyl)-2-fluoro-N-(2-(3-(methylamino)piperidin-1-yl)-5-(trifluoromethyl)phenyl)benzamide

5 Step 1: Preparation of (S)-tert-butyl methyl(1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-yl)carbamate

To an orange solution of (S)-tert-butyl 1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-ylcarbamate (1.50 g, 3.9
10 mmol) in DMF at 0 deg. C was added sodium hydride, 60% dispersion in mineral oil (0.19 g, 4.8 mmol). Bubbling was observed, and the solution became darker orange. After about 20 min, iodomethane (0.30 ml, 4.8 mmol) was added dropwise via syringe. The orange mixture was allowed to
15 warm to room temperature over 30 min. Water was added, followed by diethyl ether. The organics were washed 1 x H₂O, 1 x brine, dried over anhydrous Na₂SO₄, filtered, and concentrated to give (S)-tert-butyl methyl(1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-yl)carbamate as an
20 orange semi-solid which was used without further purification. MS *m/z* = 404 [M+H]⁺. Calc'd for C₁₈H₂₄F₃N₃O₄: 403.

25 Step 2: Preparation of (S)-tert-butyl 1-(2-amino-4-(trifluoromethyl)phenyl)piperidin-3-yl(methyl)carbamate

To a 100 mL RBF was added (S)-tert-butyl methyl(1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-yl)carbamate (1.75 g, 4.34 mmol) and palladium, 10wt. % on activated carbon wet (0.923 g, 0.868 mmol) under nitrogen. MeOH was added via
30 syringe, and the atmosphere was purged with hydrogen from a balloon. The reaction was allowed to stir rapidly under hydrogen for 8 h. The flask was purged with nitrogen, filtered through celite, rinsing with 100 mL MeOH, and concentrated to give (S)-tert-butyl 1-(2-amino-4-(trifluoromethyl)phenyl)piperidin-3-yl(methyl)carbamate as a
35 gray solid. MS *m/z* = 374 [M+H]⁺. Calc'd for C₁₈H₂₆F₃N₃O₂: 373.

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Step 3: Preparation of (S)-tert-butyl 1-(2-(2-fluoro-5-iodobenzamido)-4-(trifluoromethyl)phenyl)piperidin-3-yl(methyl)carbamate

5 In a vial, (S)-tert-butyl 1-(2-amino-4-(trifluoromethyl)phenyl)piperidin-3-yl(methyl)carbamate (.500 g, 1.3 mmol) was taken up in CH₂Cl₂. The solution was cooled to 0 deg. C and Triethylamine (0.24 ml, 1.7 mmol) and 2-fluoro-5-iodobenzoyl chloride (0.42 g, 1.5 mmol) were
10 added. The tube was sealed and the reaction stirred for 2 h. The reaction mixture was poured into EtOAc/1N NaOH. The organic layer was dried over anhydrous sodium sulfate and concentrated in vacuo. The resulting off-white foam (S)-tert-butyl 1-(2-(2-fluoro-5-iodobenzamido)-4-(trifluoromethyl)phenyl)piperidin-3-yl(methyl)carbamate was
15 used without further purification. MS *m/z* = 622 [M+H]⁺. Calc'd for C₂₅H₂₈F₄IN₃O₃: 621.

20 Step 4: Preparation of (S)-tert-butyl 1-(2-(5-(2-(2-aminopyrimidin-5-yl)ethynyl)-2-fluorobenzamido)-4-(trifluoromethyl)phenyl)piperidin-3-yl(methyl)carbamate

In a 25-mL RBF (S)-tert-butyl 1-(2-(2-fluoro-5-iodobenzamido)-4-(trifluoromethyl)phenyl)piperidin-3-yl(methyl)carbamate (.496 g, 0.80 mmol), 5-ethynylpyrimidin-
25 2-amine (0.19 g, 1.6 mmol), Bis(triphenylphosphine)palladium(II) dichloride (0.028 g, 0.040 mmol), and Copper(I) iodide (0.0076 g, 0.040 mmol) were taken up in CH₃CN and Triethylamine (1.7 ml, 12 mmol) was added, and the tube was flushed with nitrogen. The tube
30 was sealed and the reaction heated to 70 deg. C for 16 h. The reaction was cooled and transferred to a larger flask with EtOAc and concentrated in vacuo. The solid was adsorbed onto 4 g silica gel from 10% MeOH/MC purified by Isco {Redi-Sep® pre-packed silica gel column (80 g); eluent
35 0 - 75% EtOAc/hexanes over 30 min}. Product-containing fractions were concentrated to afford (S)-tert-butyl 1-(2-

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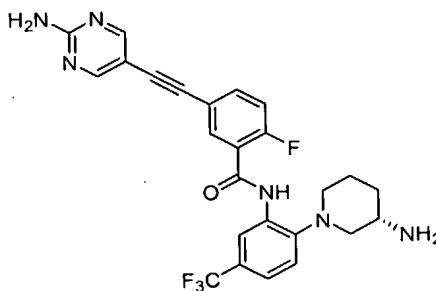
(5-(2-(2-aminopyrimidin-5-yl)ethynyl)-2-fluorobenzamido)-4-(trifluoromethyl)phenyl)piperidin-3-yl(methyl)carbamate as an orange foam. MS m/z = 613 $[M+H]^+$. Calc'd for $C_{31}H_{32}F_4N_6O_3$: 612.

5 Step 5: Preparation of (S)-5-(2-(2-aminopyrimidin-5-yl)ethynyl)-2-fluoro-N-(2-(3-(methylamino)piperidin-1-yl)-5-(trifluoromethyl)phenyl)benzamide

To a yellow solution of (S)-tert-butyl 1-(2-(5-(2-(2-aminopyrimidin-5-yl)ethynyl)-2-fluorobenzamido)-4-(trifluoromethyl)phenyl)piperidin-3-yl(methyl)carbamate
 10 (.397 g, 0.65 mmol) in 3 mL dioxane at 0 deg. C was added hydrogen chloride 4.0 M in dioxane (1.6 mL, 6.5 mmol). The reaction was allowed to warm to ambient temp, as the clump, which formed would not go into solution. 3 mL of CH_2Cl_2 ,
 15 was added followed by 5 mL MeOH to give a homogenous yellow solution. After 30 min, the solution was concentrated in vacuo to give a yellow solid, which was treated with 1N NaOH and EtOAc. The organic layer was washed twice with 1N NaOH, dried over anhyd. Na_2SO_4 , filtered, and concentrated in
 20 vacuo to give (S)-5-(2-(2-aminopyrimidin-5-yl)ethynyl)-2-fluoro-N-(2-(3-(methylamino)piperidin-1-yl)-5-(trifluoromethyl)phenyl)benzamide as a light yellow solid. MS m/z = 513 $[M+H]^+$. Calc'd for $C_{26}H_{24}F_4N_6O$: 512.

Example 77-V-4

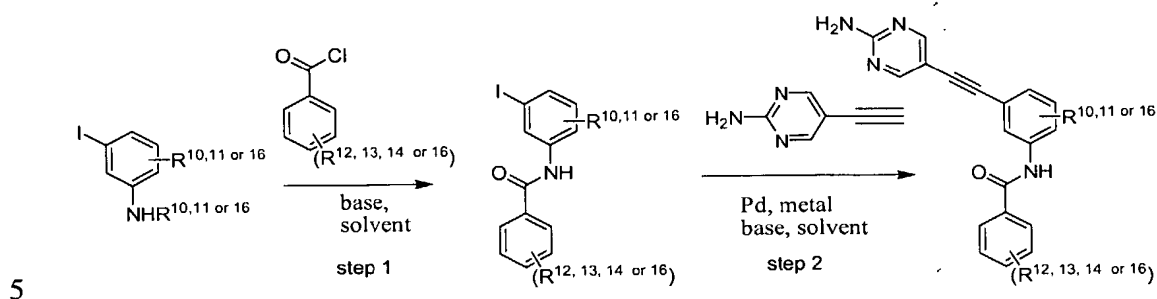
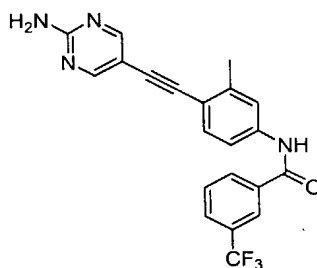
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30 **Synthesis of (S)-N-(2-(3-aminopiperidin-1-yl)-5-(trifluoromethyl)phenyl)-5-(2-(2-aminopyrimidin-5-yl)ethynyl)-2-fluorobenzamide**

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The title compound was synthesized in a manner analogous to that described in Example 77-V-3. MS m/z = 499 $[M+H]^+$.
Calc'd for $C_{25}H_{22}F_4N_6O$: 498.

Experimental Method B**Example 78**

10

Synthesis of N-(4-(2-(2-aminopyrimidin-5-yl)ethynyl)-3-methylphenyl)-3-(trifluoromethyl)benzamide

15 Step 1: Preparation of N-(4-iodo-3-methylphenyl)-3-(trifluoromethyl)benzamide

To a solution of 4-iodo-3-methyl aniline (200 mg, 0.86 mmol) and iPr_2NEt (0.19 mL, 0.95 mmol) in CH_2Cl_2 (10 mL) was added 3-(trifluoromethyl)benzoyl chloride (0.133 mL, 0.90 mmol). The mixture was allowed to stir at room temperature for 0.5 h at which time it was diluted with CH_2Cl_2 (20 mL). The organic layer was washed with aq. HCl (10 mL, 1 M), 9% aq. Na_2CO_3 (10 mL), brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure.

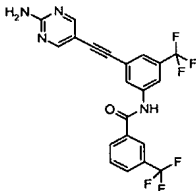
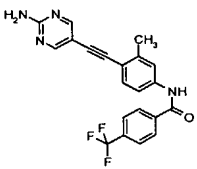
25 The resulting oil was used without further purification.

Step 2: N-(4-(2-(2-aminopyrimidin-5-yl)ethynyl)-3-methylphenyl)-3-(trifluoromethyl)benzamide

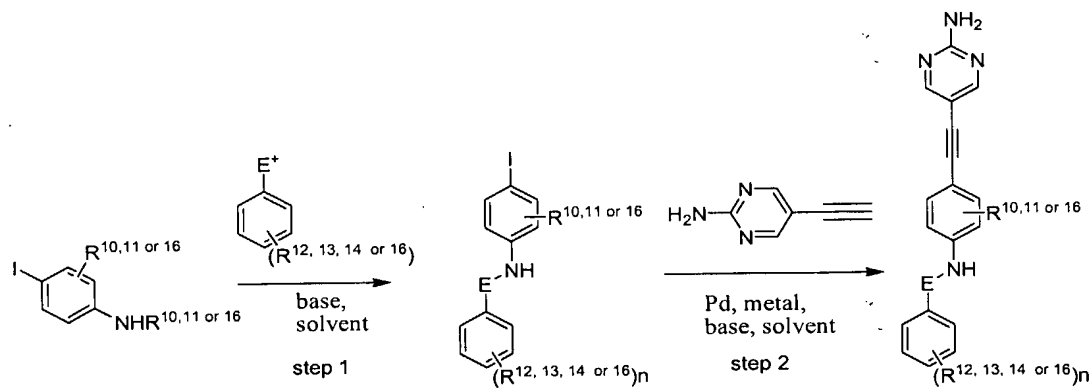
- 119 -

The title compound was prepared in a manner similar to that described Experimental Method A1, Example 1-step 2. MS $m/z = 397$ $[M+H]^+$. Calc'd for $C_{21}H_{15}F_3N_4O$: 396

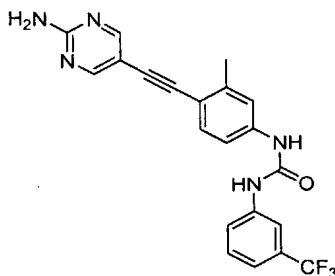
The following Examples 79-80 were prepared by a method similar to that described in Experimental Method B and Example 78.

Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
79		B1	450.34	451	
80		B1	396.37	397	

Experimental Method C1



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Example 81

5 **Synthesis of 1-(4-(2-(2-aminopyrimidin-5-yl)ethynyl)-3-methylphenyl)-3-(3-(trifluoromethyl)phenyl)urea**

Step 1: 1-(4-iodo-3-methylphenyl)-3-(3-(trifluoromethyl)phenyl)urea

10

To a solution of 4-iodo-3-methylaniline (200 mg, 0.86 mmol) in benzene (5 mL) in a sealable tube was added 1-isocyanato-3-(trifluoromethyl)benzene (0.133 mL, 0.94 mL; "E" is an electrophilic group discussed in scheme 3, and here is an isocyanate). The tube was sealed and heated at 90° C for 4 h. The mixture was allowed to cool to room temperature before filtering. The off white solid was washed with additional benzene (10 mL) and used without further purification.

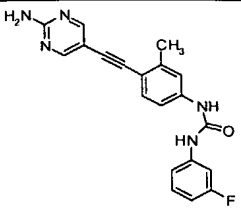
15

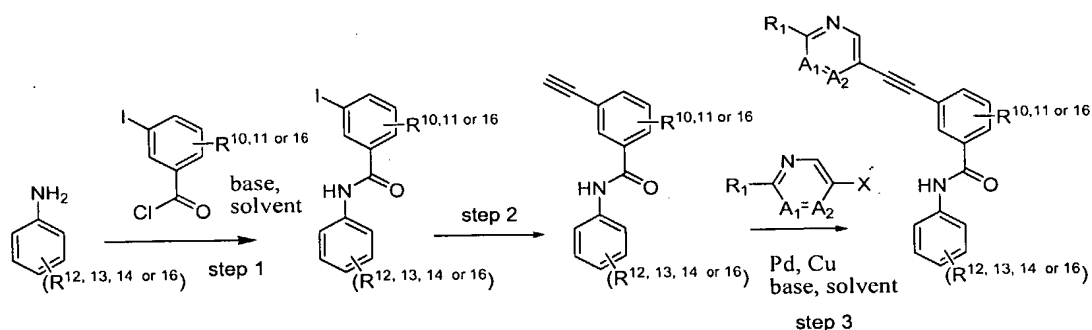
20 Step 2: 1-(4-(2-(2-aminopyrimidin-5-yl)ethynyl)-3-methylphenyl)-3-(3-(trifluoromethyl)phenyl)urea

The title compound was prepared in a manner similar to that described Experimental Method A1, Example 1-step 2. MS
25 $m/z = 412$ $[M+H]^+$. Calc'd for $C_{21}H_{16}F_3N_5O$: 411

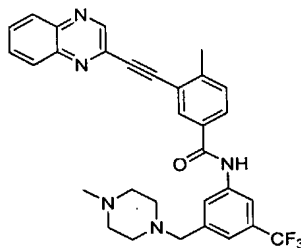
The following Example 82 was prepared by a method similar to that described in Experimental Method C1 and Example 81.

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Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
82		C1	361.38	362	

Experimental Method D

5

Example 83

- 10 **Synthesis of 4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-3-(2-(quinoxalin-2-yl)ethynyl)benzamide**

- 15 Step 1.: Preparation of 3-iodo-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)benzamide

The title compound was made in manner similar to that described in Example 2, Step 1.

- 20 Step 2: Preparation of 3-ethynyl-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)benzamide

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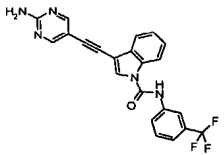
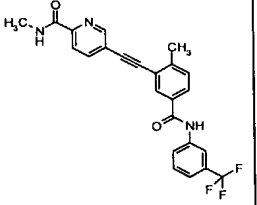
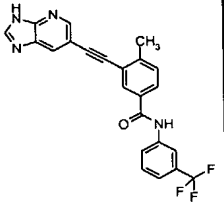
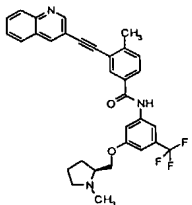
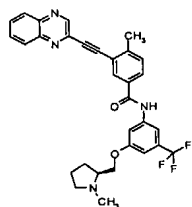
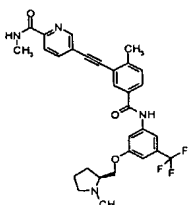
To a mixture of 3-iodo-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)benzamide (951 mg, 1.84 mmol), PdCl₂(PPh₃)₂ (65 mg, 0.092 mmol) in MeCN (75 mL) and Et₃N (20 mL) at room temperature was added trimethylsilylacetylene (0.8 mL, 5.52 mmol) followed by CuI (18 mg, 0.092 mmol). The resulting mixture was allowed to stir at room temperature for 2 h at which time the reaction mixture was concentrated under reduced pressure followed by reconstitution in MeOH (100 mL). To this mixture was added enough K₂CO₃ to saturate the mixture and the mixture was allowed to stir for about 1.5 h. The mixture was filtered through a pad of Celite. To the filtrate was added silica gel (~20 mL) and the mixture was concentrated under reduced pressure, and purified via automated flash chromatography (silica gel, 0% to 15% MeOH in CH₂Cl₂, gradient elution) to afford 3-ethynyl-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)benzamide.

Step 3: 4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)-3-(2-(quinoxalin-2-yl)ethynyl)benzamide

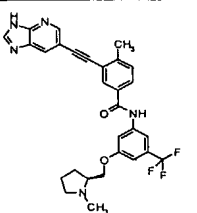
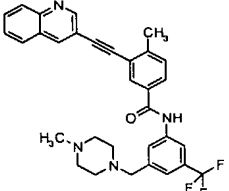
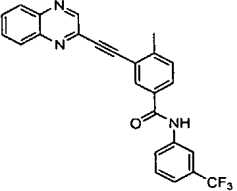
To a solution of 2-bromoquinoxaline (96 mg, 0.46 mmol), 3-3-ethynyl-4-methyl-N-(3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)phenyl)benzamide (174 mg, 0.42 mmol), PdCl₂(PPh₃)₂ (15 mg, 0.021 mmol) in MeCN (10 mL) and Et₃N (3 mL) in a sealable tube was added CuI (4 mg, 0.021 mmol). The tube was sealed and heated at 90° C for 1 h. The reaction mixture was cooled to room temperature and concentrated under reduced pressure. The resulting solid was absorbed onto silica gel (5 mL) and purified via automated flash chromatography (silica gel, 0 to 5% MeOH in CH₂Cl₂, gradient elution) to afford 4-methyl-3-(2-(quinolin-3-yl)ethynyl)-N-(3-(trifluoromethyl)phenyl)benzamide. MS m/z = 544 [M+H]⁺. Calc'd for C₃₁H₂₈F₃N₅O: 543

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The following Examples 84-92 were prepared by a method similar to that described in Experimental Method D and Example 83.

Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
84		D1	421.38	422	
85		D1	437.42	438	
86		D1	420.39	421	
87		D1	543.59	544	
88		D1	544.57	545	
89		D1	550.58	551	

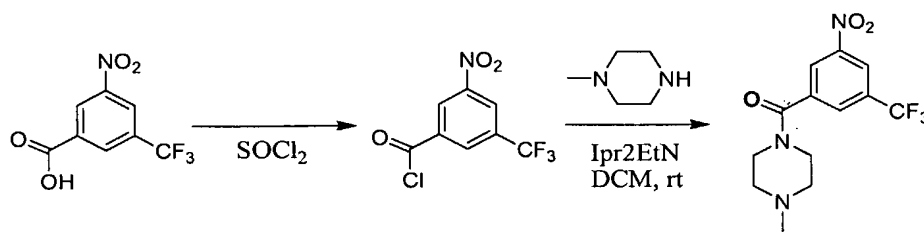
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Example No.	Structure	Method	MW	MS Data M+1	MS Data M-1
90		D1	533.55	534	
91		D1	542.6	543	
92		D1	431	432	

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Provided below are exemplary building block starting materials and intermediates, generally not commercially available, which may be utilized in Experimental Methods A-D above. Below are procedures and examples for building various of the exemplary building blocks.

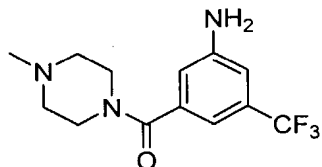
Various different A rings (R^{11} and R^{14} groups), which are contemplated herein, may be made by various methods, as represented by Examples 93-160 below.

Example 93**Synthesis of (4-methylpiperazin-1-yl)(3-nitro-5-trifluoromethylphenyl)-methanone**

- 15 Step 1: A solution of thionyl chloride (30 ml) and 3-nitro-5-(trifluoromethyl)benzoic acid (10 g) was heated to reflux for 2 h. The reaction mixture was concentrated under reduced pressure and azeotroped with toluene (10 ml - removed under reduced pressure) to afford 3-nitro-5-
- 20 (trifluoromethyl)benzoyl chloride.
- Step 2: To a solution of 3-nitro-5-(trifluoromethyl)benzoyl chloride (2.35 g, 9.3 mmol) in CH_2Cl_2 (40 ml) at room temperature was added *N*-methylpiperazine (1.26 ml, 9.3 mmol) and the mixture was allowed to stir for 30 min. The reaction
- 25 was concentrated under reduced pressure, taken up in 1 M HCl (50 ml) and the aqueous layer was washed with Et_2O (2 x 20 ml). The aqueous layer was basified to a pH of about 9 with 6N NaOH and extracted with Et_2O (3 x 50 ml). The organic extracts were combined and washed with water (1 x 20 ml)
- 30 followed by brine (1 x 20 ml), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford (4-methylpiperazin-1-yl)(3-nitro-5-

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trifluoromethyl)phenyl)-methanone as a tan oil. MS m/z = 318 $[M+H]^+$; Calc'd for $C_{13}H_{14}F_3N_3O_3$: 317.3.

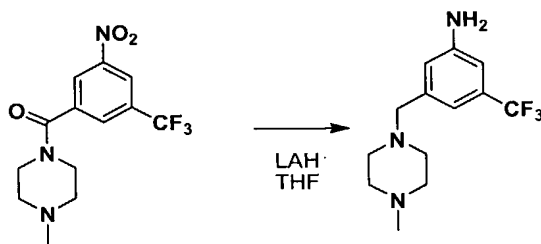
Example 94

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Synthesis of (3-amino-5-(trifluoromethyl)phenyl)(4-methylpiperazin-1-yl)methanone

To an argon purged solution of (4-methylpiperazin-1-yl)(3-nitro-5-trifluoromethyl)phenyl)-methanone (1.03 g, 3.25 mmol) was added Pd/C (344 mg, 0.32 mmol, 10%). The mixture was placed under an atmosphere of H_2 for 5 h. The reaction was purged with argon and filtered through Celite. The filtrate was concentrated under reduced pressure to afford (3-amino-5-(trifluoromethyl)phenyl)(4-methylpiperazin-1-yl)methanone as an off-white solid. MS m/z = 288.1 $[M+H]^+$. Calc'd for $C_{13}H_{16}F_3N_3O$: 287.3.

15

Example 95

20

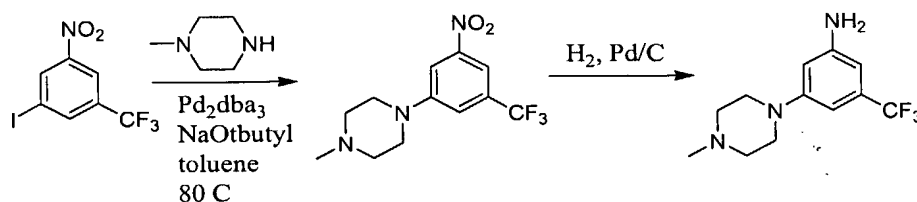
Synthesis of 3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)-benzenamine

To LAH (1.84 g, 48.5 mmol) in THF (50 ml) at room temperature was added (4-methylpiperazin-1-yl)(3-nitro-5-trifluoromethyl)phenyl)-methanone (1.54 g, 4.85 mmol) in THF (10 ml). The resulting mixture was refluxed for 5 h. The reaction mixture was cooled to 0°C at which point water (1.84 ml), 15% aq. NaOH (1.84 ml) and water (3.68 ml) were

25

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successively added. The resulting mixture was allowed to stir at room temperature for 1 h. The mixture was filtered through Celite, concentrated under reduced pressure and purified via flash chromatography (silica gel, 0 to 25% MeOH in CH₂Cl₂, gradient elution) to afford 3-((4-methylpiperazin-1-yl)methyl)-5-(trifluoromethyl)benzenamine as a colorless oil. MS *m/z* = 274 [M+H]⁺; Calc'd for C₁₃H₁₆F₃N₃O: 273.3.

Example 96

Synthesis of 3-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)benzenamine

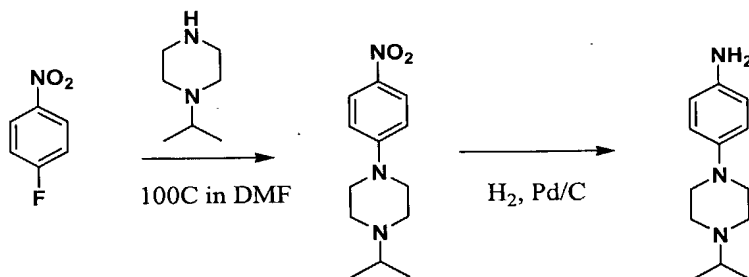
Step 1: Preparation of 1-methyl-4-(3-nitro-5-(trifluoromethyl)phenyl)piperazine

Into a 50 mL round bottom flask was placed the 1-iodo-3-nitro-5-(trifluoromethyl)benzene (1 g, 3.15 mmol), N-methylpiperazine (0.379g, 3.78 mmol), bis(dibenzylideneacetone)palladium (0.029 g, 0.0315 mmol), sodium *tert*-butoxide (0.424 g, 4.416 mmol), 2-dicyclohexyl-2'-(*N,N*-dimethylamino)biphenyl (0.037 g, 0.094 mmol), and toluene (25 mL). Reaction was heated to 80°C with stirring for 20 hours. Reaction was cooled to room temperature and water (1 mL) and ethyl acetate (10 mL) were added. The organic layer is separated, concentrated under reduced pressure and purified via silica column eluting with 0 to 20% methanol in dichloromethane. The title compound was obtained as an orange oil.

Step 2. Preparation of 3-(4-methylpiperazin-1-yl)-5-(trifluoromethyl)benzenamine

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Into a 100 mL round bottom flask under inert atmosphere was placed 1-methyl-4-(3-nitro-5-(trifluoromethyl)phenyl)piperazine (0.736 g, 2.54 mmol), 10% palladium on carbon (90 mg), ethanol (40 mL), and acetic acid (20 mL). The atmosphere was exchanged with hydrogen gas via balloon. The reaction was allowed to stir 3 days at room temperature, then filtered through celite and concentrated under reduced pressure to afford the crude as an orange oil. The crude mixture was purified via silica column chromatography with a solvent solution of 90%/10%/1% ratio of $\text{CH}_2\text{Cl}_2/\text{CH}_3\text{OH}/\text{NH}_4\text{OH}$, to afford the title compound. MS m/z = 260 $[\text{M}+\text{H}]^+$; Calc'd for $\text{C}_{12}\text{H}_{16}\text{F}_3\text{N}_3$: 259.3.

Example 97**Step 1: Synthesis of 1-isopropyl-4-(4-nitrophenyl)piperazine**

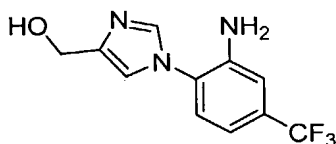
To a vial was added 4-fluoronitrobenzene (1.41 g, 1.06 mmol), N,N-diisopropylethylamine (1.92 mL, 0.011 mmol), isopropylpiperazine (1.41g, 0.011 mmol), and N,N-dimethylformamide (10 mL). Mixture was heated at 100°C for 48 h in a sealed tube. The reaction mixture was cooled to room temperature and concentrated. The residue was purified via silica gel column chromatography (gradient elution with 0 to 10% methanol in dichloromethane) to afford 1-isopropyl-4-(4-nitrophenyl)piperazine.

Step 2: Synthesis of 4-(4-isopropylpiperazin-1-yl)benzenamine

10% Palladium on carbon (0.05 g) was added to a solution of the nitroaniline (0.001 mol) in ethanol (50 mL)

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under a H₂(g) atmosphere (via balloon). The reaction mixture stirred at RT overnight and then filtered through celite. The filtrate was concentrated to afford a dark yellow oil, which was purified via silica column chromatography using an isocratic solvent system of 100% (90/10/1) (CH₂Cl₂/CH₃OH/NH₄OH) to isolate the title compound. MS m/z = 220 [M+H]⁺; Calc'd for C₁₃H₂₁N₃: 219.3.

Example 98**Synthesis of (1-(2-amino-4-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)methanol****Step 1: (1-(2-nitro-4-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)methanol**

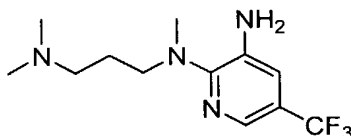
To a solution of 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (1.04 mL, 7.43 mmol) and (1H-pyrrol-3-yl)methanol hydrochloride salt (1.0 g, 7.43 mmol) in DMF (10 mL) was added Na₂CO₃ (2.36 g, 22.3 mmol). The resulting mixture was heated at 70°C overnight. The mixture was cooled to room temperature and concentrated under reduced pressure. The mixture was reconstituted in EtOAc (50 mL) and washed with 9% aq. Na₂CO₃ (10 mL), brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford (1-(2-nitro-4-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)methanol.

Step 2: (1-(2-amino-4-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)methanol

To a solution of (1-(2-nitro-4-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)methanol (167 mg, 0.58 mmol) in EtOH (10 mL) was added a slurry of Raney Nickel (500 mg, washed, wet). The mixture was allowed to

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stir at room temperature overnight. Upon completion, the reaction mixture was filtered through Celite and concentrated to afford (1-(2-amino-4-(trifluoromethyl)phenyl)-1H-imidazol-4-yl)methanol. MS m/z = 258 $[M+H]^+$. Calc'd for $C_{11}H_{10}F_3N_3O$: 257.

Example 99

10 **Synthesis of N^2 -(3-(dimethylamino)propyl)- N^2 -methyl-5-(trifluoromethyl)pyridine-2,3-diamine**

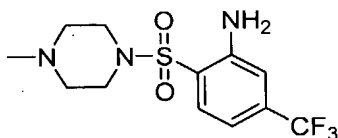
Step 1: N-(3-(dimethylamino)propyl)-N-methyl-3-nitro-5-(trifluoromethyl)pyridin-2-amine

15 A solution of 3-nitro-5-(trifluoromethyl)pyridin-2-ol (500 mg, 2.4 mmol), $CHCl_3$ (25 mL), oxalyl chloride (0.42 mL, 4.8 mmol) and DMF (1 drop) was allowed to reflux for 16 h. Once consumption of starting material was complete the reaction was concentrated under reduced pressure. A portion of the crude material (182 mg, 0.8 mmol) was removed and added to a mixture of N^1,N^1,N^3 -trimethylpropane-1,3-diamine (0.13 mL, 0.88 mmol), K_2CO_3 (221 mg, 1.6 mmol) and heated at 90°C for 10 min. The mixture was concentrated under reduced pressure and reconstituted in CH_2Cl_2 (20 mL). The organic layer was washed with water (10 mL), brine (10 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford N-(3-(dimethylamino)propyl)-N-methyl-3-nitro-5-(trifluoromethyl)pyridin-2-amine. MS m/z = 307 $[M+H]^+$. Calc'd for $C_{12}H_{17}F_3N_4O_2$: 306.

Step 2: N^2 -(3-(dimethylamino)propyl)- N^2 -methyl-5-(trifluoromethyl)pyridine-2,3-diamine

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To a solution of N-(3-(dimethylamino)propyl)-N-methyl-3-nitro-5-(trifluoromethyl)pyridin-2-amine (246 mg, 0.8 mmol) in EtOH was added Raney Nickel (700 mg, wet, washed). The reaction was allowed to stir for 2 h then filtered through a pad of Celite and concentrated under reduced pressure to afford N²-(3-(dimethylamino)propyl)-N²-methyl-5-(trifluoromethyl)pyridine-2,3-diamine. MS *m/z* = 277 [M+H]⁺. Calc'd for C₁₂H₁₉F₃N₄: 276

Example 100**Synthesis of 2-(4-methylpiperazin-1-ylsulfonyl)-5-(trifluoromethyl)benzenamine**

15 Step 1: 1-methyl-4-(2-nitro-4-(trifluoromethyl)phenylsulfonyl)piperazine

To a solution of 2-nitro-4-(trifluoromethyl)benzene-1-sulfonyl chloride (1.0 g, 1.73 mmol) in CH₂Cl₂ (50 mL) was added 1-methylpiperazine (0.40 mL, 3.6 mmol). The resulting mixture was allowed to stir at room temperature overnight, then diluted with CH₂Cl₂ (30 mL), the organic layer was washed with 9% aq. Na₂CO₃ (10 mL) and brine (10 mL). The organic layer was dried over anhydrous sodium sulfate, filtered and concentrated to afford the title compound as a white solid.

25 Step 2: 2-(4-methylpiperazin-1-ylsulfonyl)-5-(trifluoromethyl)benzenamine

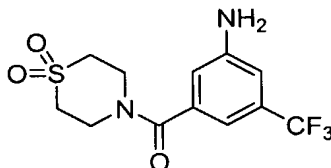
30 1-methyl-4-(2-nitro-4-(trifluoromethyl)phenylsulfonyl)piperazine was dissolved in EtOH (20 mL) and the solution was purged with argon. Pd/C (365 mg, 0.34 mmol, 10%) was added to the solution, which was stirred for 3 days in an atmosphere of hydrogen gas. The mixture was again purged with argon, filtered through Celite

35

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and concentrated under reduced pressure to afford 2-(4-methylpiperazin-1-ylsulfonyl)-5-(trifluoromethyl)benzenamine. MS m/z = 324 $[M+H]^+$. Calc'd for $C_{12}H_{16}F_3N_3O_2S$: 323.

5

Example 101**Synthesis of (3-amino-5-(trifluoromethyl)phenyl)(sulfonylmorpholino)methanone**

10

Step 1: (3-nitro-5-(trifluoromethyl)phenyl)(thiomorpholino)methanone

3-Nitro-5-(trifluoromethyl)benzoic acid (2.96 g, 12.6 mmol) was allowed to reflux in thionyl chloride (6 mL) for 6 h. The resulting solution was allowed to cool to room temperature and then concentrated under reduced pressure. The resulting solid was taken up in CH_2Cl_2 (20 mL) and iPr_2Net (2.6 mL, 15.1 mmol) and thiomorpholine (1.4 mL, 13.8 mmol) was added. The reaction was stirred at RT for 1 h and then diluted with CH_2Cl_2 (50 mL). The organic layer was washed with aq. HCl (1M, 25 mL), 9% aq. Na_2CO_3 (25 mL), brine, dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford (3-nitro-5-(trifluoromethyl)phenyl)(thiomorpholino)-methanone.

25

Step 2: (3-nitro-5-(trifluoromethyl)phenyl)(sulfonylmorpholino)-methanone

To a solution of (3-nitro-5-(trifluoromethyl)phenyl)-(thiomorpholino)methanone (1.56 g, 4.88 mmol) in EtOH (50 mL) was added a solution of ammonium molybdate tetrahydrate (602 mg, 0.49 mmol) and hydrogen peroxide (30%, 4.2 mL, 43.92 mmol). The resulting mixture was allowed to stir overnight. Once the reaction was complete, as observed by TLC (1:1 hexanes:EtOAc), it was poured onto water (100 mL).

35

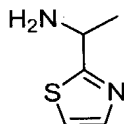
- 133 -

The aqueous layer was extracted with CH_2Cl_2 (3 x 50 mL). The combined organic layers were washed with water (25 mL), brine (25 mL), dried over anhydrous sodium sulfate, filtered and concentrated under reduced pressure to afford (3-nitro-5-(trifluoromethyl)phenyl)(sulfonylmorpholino)methanone.

Step 3: (3-amino-5-(trifluoromethyl)phenyl)(sulfonylmorpholino)-methanone

To an argon purged solution of (3-nitro-5-(trifluoromethyl)phenyl)-(sulfonylmorpholino) methanone (658 mg, 1.87 mmol) in EtOH (20 mL) was added Pd/C (198 mg, 0.187 mmol, 10%). The resulting mixture was allowed to stir under an atmosphere of hydrogen gas for 3 days. The reaction was purged with argon, filtered through Celite and concentrated under reduced pressure to afford (3-amino-5-(trifluoromethyl)phenyl)-(sulfonylmorpholino)methanone which was used without further purification. MS m/z = 323 $[\text{M}+\text{H}]^+$. Calc'd for $\text{C}_{12}\text{H}_{13}\text{F}_3\text{N}_2\text{O}_3\text{S}$: 322.

Example 102



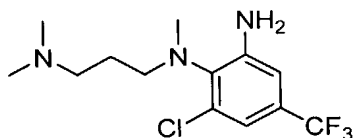
Synthesis of 1-(thiazol-2-yl)ethanamine

The title compound was prepared by a procedure similar to that described in *J. Chem. Soc. Perkin trans.*, 2, 1339, 2000 (also described in PCT Intl. Patent Publication No. WO 2003093238 A1). NH_4OAc (38.54 g, 500 mmol) was added to 1-(thiazol-2-yl)ethanone (5.0 g, 39.3 mmol) in MeOH (100 mL). The mixture was stirred at RT for 15 min. NaCNBH_4 (1.76 g, 200 mmol) was added and the mixture was stirred for 4 d. 30 mL 6N HCl was added dropwise with the formation of a solid precipitate. The white solid was isolated by filtration then taken up in H_2O and washed with Et_2O . The aqueous solution was then basified to pH of about 10 with NaOH,

- 134 -

Extracted with EtOAc and dried over Na₂SO₄. Purification by silica chromatography eluting with 5% MeOH/CH₂Cl₂ afforded 1-(thiazol-2-yl)ethanamine. MS *m/z* = 129 [M+H]⁺. Calc'd for C₅H₈N₂S: 128

5

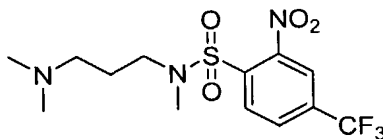
Example 103

10 **Synthesis of 6-chloro-N¹-(3-(dimethylamino)propyl)-N¹-methyl-4-(trifluoromethyl)benzene-1,2-diamine**

A heterogeneous mixture of 1-chloro-2-fluoro-3-nitro-5-(trifluoromethyl)benzene (1.25 mL, 8.2 mmol), K₂CO₃ (3.44 g, 24.6 mmol), N¹,N¹,N³-trimethylpropane-1,3-diamine (1.26 mL, 8.61 mmol) and THF were allowed to stir at room temperature for 45 min. The THF was removed under reduced pressure and reconstituted in EtOAc (50 ml). The organic layer was washed with water (20 ml), brine (20 ml), dried over anhydrous sodium sulfate, filtered and concentrated to an oil. The concentrated oil was taken up in EtOH (20 ml) to which Raney nickel (2.5 g wet, washed) was added. The reduction was monitored and after 1 h, another portion of Raney nickel (3.8 g, wet, washed) was added. The reaction was allowed to stir for an additional 30 min., and filtered through Celite, washed with EtOH (10 ml) and concentrated. The crude residue was purified via flash chromatography (silica gel, gradient elution 0 to 25% MeOH in CH₂Cl₂) to afford 6-chloro-N¹-(3-(dimethylamino)propyl)-N¹-methyl-4-(trifluoromethyl)benzene-1,2-diamine as a yellow oil. MS *m/z* = 310.1 [M+H]⁺. Calc'd for C₁₃H₁₉ClF₃N₃: 309.8.

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20
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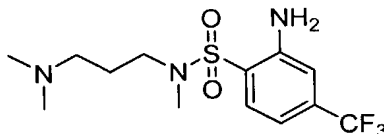
- 135 -

Example 104**Synthesis of *N*-(3-(dimethylamino)propyl)-*N*-methyl-2-nitro-4-(trifluoromethyl)benzenesulfonamide**

5

To a solution of 2-nitro-4-(trifluoromethyl)benzene-1-sulfonyl chloride (500 mg, 1.73 mmol) in CH₂Cl₂ (5 ml) was added *N*¹,*N*¹,*N*³-trimethylpropane-1,3-diamine (0.26 ml, 1.8 mmol). The resulting mixture was allowed to stir at room temperature for 20 min. Diluted with CH₂Cl₂ (30 ml) and washed the organic layer with 9% aq. Na₂CO₃ (10 ml) and brine (10 ml). Dried over anhydrous sodium sulfate, filtered and concentrated to a white solid, which was used without further purification. MS *m/z* = 370.1 [M+H]⁺. Calc'd for C₁₃H₁₈F₃N₃O₄S: 369.4.

15

Example 105**Synthesis of 2-amino-*N*-(3-(dimethylamino)propyl)-*N*-methyl-4-(trifluoromethyl)benzenesulfonamide**

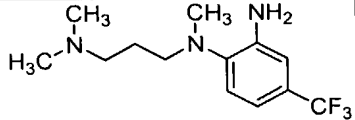
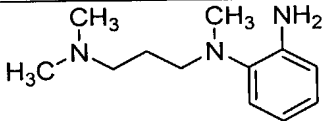
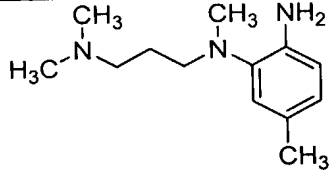
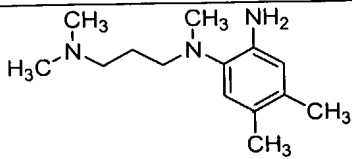
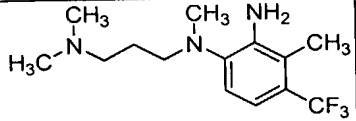
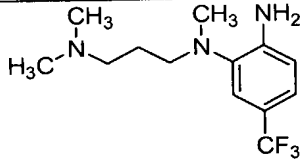
20

To an argon purged solution of *N*-(3-(dimethylamino)propyl)-*N*-methyl-2-nitro-4-(trifluoromethyl)benzenesulfonamide (255 mg, 0.69 mmol) in EtOH (10 ml) was added Pd/C (73 mg, 0.069 mmol, 10%). The reaction mixture was placed under an atmosphere of H₂ gas and allowed to stir for 2 h. The reaction mixture was purged with argon and filtered through Celite. The reaction was washed with EtOH (10 ml) and concentrated under reduced pressure to afford 2-amino-*N*-(3-(dimethylamino)propyl)-*N*-methyl-4-(trifluoromethyl)benzenesulfonamide as a dark oil. MS *m/z* = 340.1 [M+H]⁺. Calc'd for C₁₃H₂₀F₃N₃O₂S: 339.4.

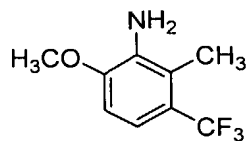
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The following substituted aniline intermediates were prepared in a manner similar to the procedures described in Examples 93-105 and Example 55 of co-pending patent Application serial no. 60/569,193:

Example	Structure	Name	Cal'd MS	M+H ⁺
106		N1-(3-(dimethylamino)propyl)-N1-methyl-4-(trifluoromethyl)benzene-1,2-diamine:	275	276 .1
107		N1-(3-(dimethylamino)propyl)-N1-methylbenzene-1,2-diamine	207	208
108		N1-(3-(dimethylamino)propyl)-N1,5-dimethylbenzene-1,2-diamine:	221	222
109		N1-(3-(dimethylamino)propyl)-N1,4,5-trimethylbenzene-1,2-diamine:	235	236
110		N1-(3-(dimethylamino)propyl)-N1,3-dimethyl-4-(trifluoromethyl)benzene-1,2-diamine:	289	290
111		N1-(3-(dimethylamino)propyl)-N1-methyl-5-(trifluoromethyl)benzene-1,2-diamine:	275	276

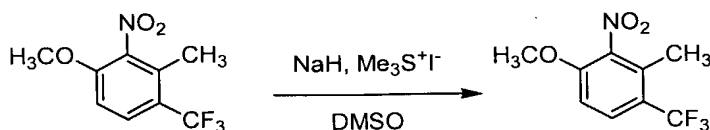
- 137 -

Example 112

5 **Synthesis of 6-methoxy-2-methyl-3-(trifluoromethyl)benzenamine**

Step 1: 1-methoxy-3-methyl-2-nitro-4-(trifluoromethyl)benzene

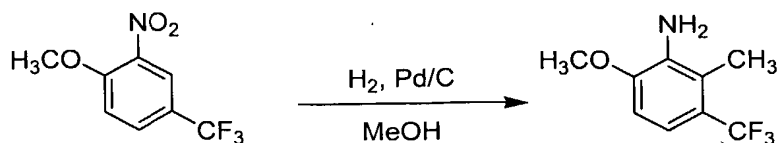
10



1-methoxy-3-methyl-2-nitro-4-(trifluoromethyl)benzene was prepared by a procedure similar to that described in "Synthesis of 3,6-Disubstituted 2-Nitrotoluenes by Methylation of Aromatic Nitro Compounds with Dimethylsulfonium Methylide", Kitano, Masafumi, Ohashi Naohito, *Synthetic Communications*, 30(23), 4247-4254, 2000. To a suspension of NaH (60% by wt. in mineral oil, 362 mg, 9.04 mmol) and trimethylsulfonium iodide (1.84 g, 9.04 mmol) in DMSO (17 ml) and THF (6.7 ml) was added 4-methoxy-3-nitrobenzotrifluoride (1.00 g, 4.52 mmol) as a solution in DMSO (2.7 ml). The reaction mixture was allowed to stir at 10-20°C for 5 hrs. The reaction mixture was quenched by addition to ice water. The aqueous layer was separated and extracted with toluene 7 times. The combined organic extracts were washed with brine, dried over MgSO₄, and filtered. The solvent was removed by distillation at reduced pressure. The residue was purified by automated silica gel chromatography (100% hexanes to 98:2 hexanes:ethylacetate) to provide 1-methoxy-3-methyl-2-nitro-4-(trifluoromethyl)benzene.

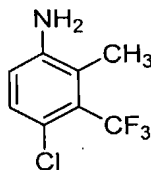
Step 2: 6-methoxy-2-methyl-3-(trifluoromethyl) benzenamine

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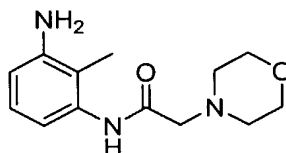
1-methoxy-3-methyl-2-nitro-4-(trifluoromethyl)benzene
 5 (258 mg, 1.10 mmol), methanol (11.0 mL), and palladium on
 carbon (77.4 mg) were combined in a N₂-purged round bottom
 flask. A balloon containing H₂ was affixed to the flask,
 and the solution was saturated with H₂ for 2 minutes. The
 reaction mixture was allowed to stir under H₂ atmosphere for
 10 12 hrs. Upon completion, as judged by LCMS, the reaction
 mixture was filtered through a plug of Celite and the
 solvent was removed *in vacuo* to afford 6-methoxy-2-methyl-3-
 (trifluoromethyl) benzenamine. MS *m/z* = 206 [M+H]⁺. Calc'd
 for C₉H₁₀F₃NO: 205.

15

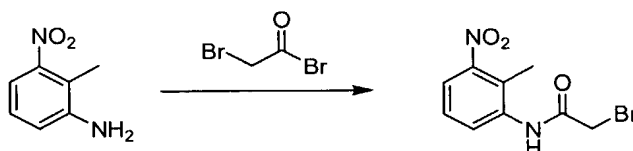
Example 113**Synthesis of 4-chloro-2-methyl-3-(trifluoromethyl)benzenamine**

20 4-Chloro-2-methyl-3-(trifluoromethyl)benzenamine was
 prepared by a method similar to that described in
 "Preparation of Fused Succinimides as Modulators of Nuclear
 Hormone Receptor Function", Salvati, Mark E. et al., PCT
 Patent Publication WO 2003062241. MS *m/z* = 210 [M+H]⁺.
 25 Calc'd for C₉H₁₀F₃NO: 210.

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Example 114**5 Synthesis of N-(3-amino-2-methylphenyl)-2-morpholinoacetamide**

Step 1: 2-bromo-N-(2-methyl-3-nitrophenyl)acetamide



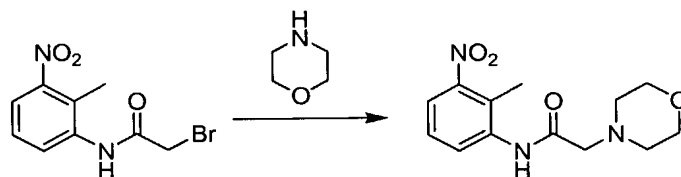
10

To a solution of 2-methyl-3-nitroaniline (5.0 g, 32.9 mmol) in 120 ml of CH_2Cl_2 was added 120 ml of saturated NaHCO_3 and bromoacetyl bromide (2.85 ml, 6.6 g, 32.9 mmol). The reaction was stirred at room temperature for 64 hours.

15 The layers were separated, and the organic layer was washed with water, brine and then dried over MgSO_4 . Solvent evaporation afforded 2-bromo-N-(2-methyl-3-nitrophenyl)acetamide as a yellow solid.

Step 2: N-(2-methyl-3-nitrophenyl)-2-morpholinoacetamide

20



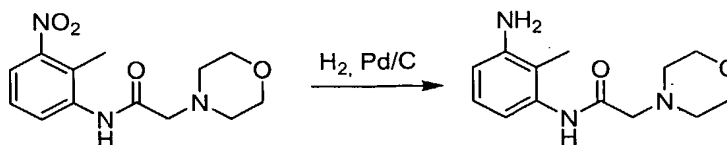
25 2-Bromo-N-(2-methyl-3-nitrophenyl)acetamide (0.5 g, 1.8 mmol) was dissolved in 15 ml of THF and to this was added morpholine (0.17g, 2.0 mmol) and diisopropylethylamine (0.71 g, 5.5 mmol). The reaction was stirred at room temperature for 16 hours. The reaction was then partitioned between EtOAc and H_2O . The aqueous mixture was extracted with EtOAc, and the combined organic layers were washed with

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H₂O, brine and then dried over MgSO₄. Solvent evaporation afforded N-(2-methyl-3-nitrophenyl)-2-morpholinoacetamide as a yellow solid.

Step 3: N-(3-amino-2-methylphenyl)-2-morpholinoacetamide

5

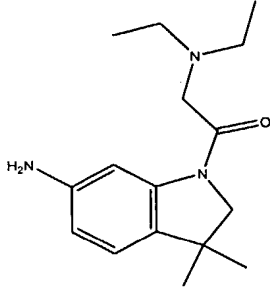
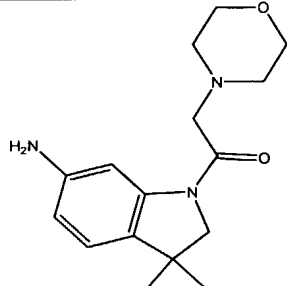


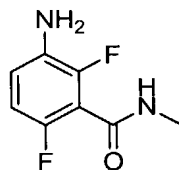
N-(2-Methyl-3-nitrophenyl)-2-morpholinoacetamide (0.25 g, 0.9 mmol) was dissolved in 20 ml of MeOH, and to this was added a slurry of 10 % Pd/C (0.025 g) in a minimal amount of EtOH. The reaction vessel was evacuated and purged with H₂, and the reaction was stirred at room temperature for 16 hours. The mixture was purged with N₂ for 30 minutes and then filtered through a pad of celite. Solvent evaporation afforded N-(3-amino-2-methylphenyl)-2-morpholinoacetamide as a gray solid. MS m/z = 250.1 [M+H]⁺; Calc'd for C₁₃H₁₉N₃O₂: 249.

Examples 115-118 were prepared by a method similar to the procedure described in Example 114 above.

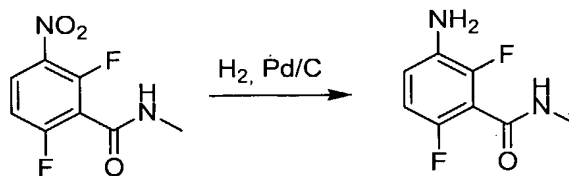
Example	Structure	Name
115		N-(5-amino-2-methylphenyl)-2-morpholinoacetamide
116		N-(3-amino-2-methylphenyl)-2-(diethylamino)acetamide

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117		1-(6-amino-3,3-dimethylindolin-1-yl)- 2-(diethylamino)ethanone
118		1-(6-amino-3,3-dimethylindolin-1-yl)- 2-morpholinoethanone

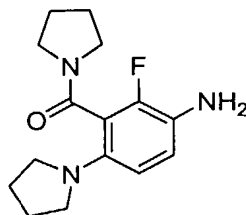
Example 119

5

Synthesis of 3-amino-2,6-difluoro-N-methylbenzamide

10 2,6-Difluoro-3-nitrophenylacetamide (0.5 g, 2.3 mmol)
 was dissolved in 20 ml of MeOH and to this was added a
 slurry of 10% Pd/C (0.050 g). The reaction vessel was
 evacuated and purged with H₂, and the reaction was stirred
 at room temperature for 3 hours. The mixture was purged with
 15 N₂, and then filtered through a pad of celite. Solvent
 evaporation afforded 3-amino-2,6-difluoro-N-methylbenzamide
 as a pink solid.

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Example 120

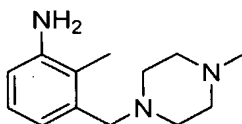
(3-amino-2-fluoro-6-(pyrrolidin-1-yl)phenyl)(pyrrolidin-1-yl)methanone

5

Example 120 was prepared by a method similar to that described in Example 119 above.

Example 121

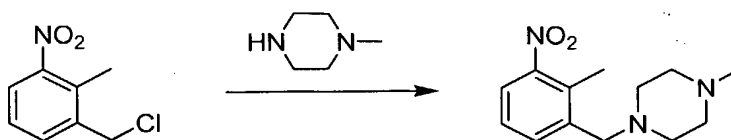
10



Synthesis of 2-methyl-3-((4-methylpiperazin-1-yl)methyl)benzeneamine

15

Step 1: 1-(2-methyl-3-nitrobenzyl)-4-methylpiperazine



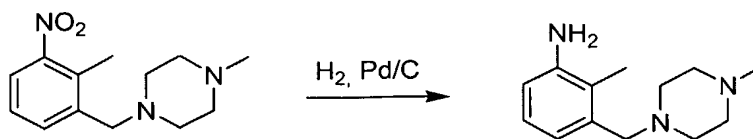
20

2-Methyl-3-nitrobenzylchloride (1.0 g, 5.4 mmol) was dissolved in 30 ml of THF, and to this was added 1-methylpiperazine (0.65 g, 6.5 mmol) and sodium bicarbonate (2.26 g, 26.9 mmol). The reaction mixture was stirred at 65 °C for 16 hours. The mixture was partitioned between EtOAc and H₂O. The aqueous layer was extracted with EtOAc, and the combined organic layers were washed with saturated NH₄Cl, H₂O, brine and dried over MgSO₄. Solvent evaporation afforded 1-(2-methyl-3-nitrobenzyl)-4-methylpiperazine.

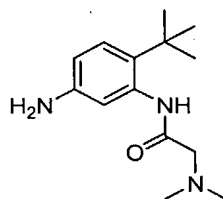
30

Step 2: 2-methyl-3-((4-methylpiperazin-1-yl)methyl)benzeneamine

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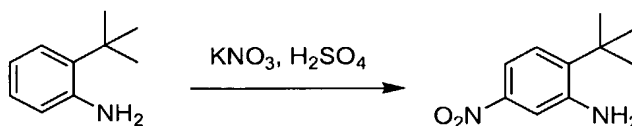


5 1-(2-Methyl-3-nitrobenzyl)-4-methylpiperazine (1.2 g, 4.8 mmol) was dissolved in 50 ml of MeOH, and to this was added a slurry of 10% Pd/C in a minimal amount of EtOH. The reaction mixture was evacuated and purged with H₂, and then stirred at room temperature for 3 hours. The mixture was
 10 purged with N₂ for 30 minutes and then filtered through a pad of celite. Solvent evaporation afforded 2-methyl-3-((4-methylpiperazin-1-yl)methyl)benzeneamine.

Example 122

Synthesis of N-(5-amino-2-tert-butylphenyl)-2-dimethylaminoacetamide

Step 1: 2-tert-butyl-5-nitrobenzenamine

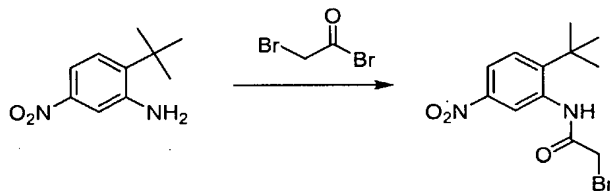


25 Concentrated sulfuric acid (1 L) was cooled to -10 °C with a dry ice-isopropanol bath in a 2 L 3-necked round bottom flask fitted with a mechanical stirrer and temperature probe. The 2-t-butylaniline (109 g, 730 mmol) was added, giving a clumpy solid. Once the temperature of
 30 the mixture was stabilized at -10 °C, the potassium nitrate (101 g, 1001 mmol) was added portion wise, as a solid, over

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a 4-hour period, maintaining the temperature between -20 and -5 °C. Once all of the potassium nitrate was added, the reaction was left to stir overnight with gradual warming to room temperature. The reaction was quenched by diluting
5 with water and then extracting three times with EtOAc. The EtOAc extracts were washed multiple times with saturated NaHCO₃, until gas evolution ceased, then with brine. The ethyl acetate extracts were then combined, dried over anhydrous Na₂SO₄, filtered and concentrated under reduced
10 pressure giving a black oil. The oil was eluted through a column of silica gel with EtOAc: hexanes gradient 5-50%. Solvent evaporation afforded 2-tert-butyl-5-nitrobenzenamine as a red solid.

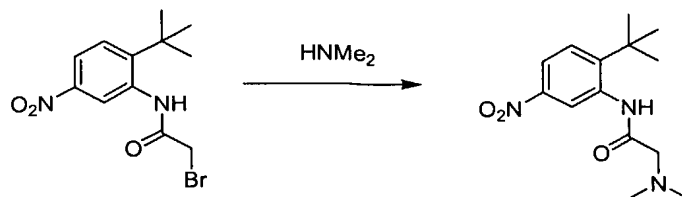
15 Step 2: 2-bromo-N-(2-tert-butyl-5-nitrophenyl)acetamide



2-tert-Butyl-5-nitrobenzenamine (70 g, 359 mmol) and a catalytic amount of DMAP were dissolved into THF (1.5 L) under N₂. Triethylamine (109 g, 1077 mmol) was added and
20 the solution was cooled to 0 °C. Bromoacetyl bromide (207 g, 1023 mmol) was then added and the reaction was stirred at room temperature for 16 hours. The reaction was then partially concentrated under reduced pressure, treated with
25 water, and extracted three times with EtOAc. The EtOAc extracts were washed with brine, combined, dried over Na₂SO₄ and concentrated to a black oil. This oil was purified using silica chromatography, 95:5:0.5 CH₂Cl₂:MeOH:NH₄OH, giving 2-bromo-N-(2-tert-butyl-5-nitrophenyl)acetamide as a
30 brown solid.

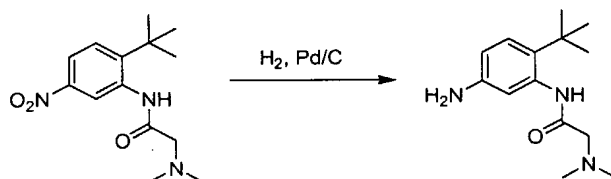
Step 3: N-(2-tert-butyl-5-nitrophenyl)-2-(dimethylamino)acetamide

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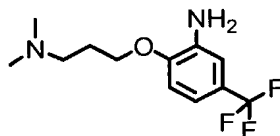
2-Bromo-N-(2-tert-butyl-5-nitrophenyl)acetamide (80 g, 253, mmol) and potassium carbonate (70 g, 506 mmol) were combined in THF (1.75 L), and the mixture was cooled to 0 °C. N,N-Dimethylamine (40 ml of a 2 M solution in THF, 800 mmol) was then added to the mixture through an addition funnel over a 30-minute period. The mixture was then stirred at room temperature for 16 hours. The mixture was then filtered and the filtrate was concentrated. The crude material was purified by silica chromatography using 50% EtOAc:hexanes as the eluent to give N-(2-tert-butyl-5-nitrophenyl)-2-(dimethylamino)acetamide as a brown solid.

15 Step 4: N-(5-amino-2-tert-butylphenyl)-2-dimethylamino)acetamide



To a solution of N-(2-tert-butyl-5-nitrophenyl)-2-(dimethylamino)acetamide in 1,4-dioxane was added 10% Pd/C as a slurry in a minimal amount of EtOH. The mixture was evacuated and purged with H₂, and then stirred at room temperature for 16 hours. The reaction was then purged with N₂ and filtered through celite. The filtrate was concentrated and purified using silica chromatography, 97.5:2.5:0.25 to 95:5:0.5 CH₂Cl₂:MeOH:NH₄OH, to afford N-(5-amino-2-tert-butylphenyl)-2-dimethylamino)acetamide as a brown solid. MS (m/z) = 250.2 (M+H⁺); Calculated for C₁₄H₂₃N₃O: 249.4

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Example 123**Synthesis of N,N-dimethyl-3-(2-nitro-4-(trifluoromethyl)phenoxy)propan-1-amine**

5

Step 1: 2-(3-(dimethylamino)propoxy)-5-(trifluoromethyl)benzenamine

A suspension of NaHCO_3 (3.9 g, 48 mmol), 1-fluoro-2-nitro-4-trifluoromethylbenzene (4.0 g, 19 mmol), and 3-dimethylamino-1-propanol (2.5 ml, 21 mmol) in 38 mL dry THF was heated with a reflux condenser under nitrogen for 12 h. The mixture was filtered through a fritted funnel into a flask. The solution was cooled to 0 °C and was treated with potassium tert-butoxide (2.4 g, 21 mmol) resulting in an orange solution. The solution was warmed to ambient temperature and was allowed to stir for 1 h. The solvent was removed in vacuo, and the resulting brown oil was partitioned between saturated aqueous NaHCO_3 and methylene chloride. The aqueous layer was extracted three times with methylene chloride. The combined organic layers were dried with Na_2SO_4 , filtered, and concentrated. The residue was purified by silica gel chromatography (MC/MeOH/conc. NH_4OH) to provide the desired compound as an orange oil. MS (m/z): 293.1 (M+H)⁺. Calc'd for $\text{C}_{12}\text{H}_{15}\text{F}_3\text{N}_2\text{O}_3$: 292.25.

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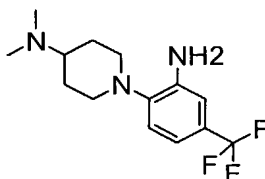
Step 2: N,N-dimethyl-3-(2-nitro-4-(trifluoromethyl)phenoxy)propan-1-amine

To 2-(3-(dimethylamino)propoxy)-5-(trifluoromethyl)benzenamine (1.6 g, 5.5 mmol) was added Pd/C (10%, 0.58 g) under nitrogen. Methanol (18 ml) was added via syringe, and H_2 gas was introduced and the mixture stirred vigorously under an atmosphere of H_2 . After 23 h, the mixture was filtered through celite and concentrated to

30

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afford the title compound as a light brown solid. MS (m/z): 263 (M+H)⁺. Calc'd for C₁₂H₁₇F₃N₂O₃: 262.27.

Example 124**5 Synthesis of 1-(2-amino-4-(trifluoromethyl)phenyl)-N,N-dimethylpiperidin-4-amine****10 Step 1: 1-benzyl-N,N-dimethylpiperidin-4-amine dihydrochloride**

To a mixture of 4-amino-1-benzyl piperidine (5.0 g, 26 mmol), NaBH₃CN (3.3 g, 53 mmol), AcOH (7.5 ml, 132 mmol) in 130 ml MeOH at 0 °C under nitrogen was added formaldehyde (37 wt % in water, 5.3 mL) as a solution in 15 ml MeOH slowly dropwise via a pressure-equalized addition funnel over 15 min. The resulting clear solution was allowed to warm to room temperature and was allowed to stir for approximately 60 h. The reaction was quenched by the addition of 20 ml saturated aqueous potassium carbonate. The mixture was concentrated in vacuo, and water and EtOAc was added. The organic layer was removed, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were dried with Na₂SO₄, filtered, and concentrated to give a cloudy oil, which was dissolved in methylene chloride and filtered through a fritted funnel. The solvent was removed to give a waxy solid, which was purified by silica gel chromatography (MC/MeOH/conc. NH₄OH). The resulting material was dissolved in diethyl ether, cooled to 0°C and treated with 20 ml 4N HCl in dioxane. The solvent was removed in vacuo to give the desired product as a white solid. MS (m/z): 219.1 (M+H)⁺. Calc'd for C₁₄H₂₂N₂: 218.34.

30 Step 2: N,N-dimethyl-1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-4-amine

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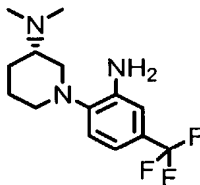
To 1-benzyl-N,N-dimethylpiperidin-4-amine dihydrochloride (6.7 g, 23 mmol) was added Pd/C (10%, 2.4 g) under argon. Methanol (100 ml) was added via syringe, and
5 H₂ gas was introduced and the mixture stirred vigorously under an atmosphere of H₂. After 48 h, the mixture was flushed with nitrogen, filtered through celite and concentrated to afford a mixture of starting material and N,N-dimethylpiperidin-4-amine dihydrochloride as a white
10 solid. This solid was treated with 1-Fluoro-2-nitro-4-trifluoromethyl-benzene (3.2 ml, 22.9 mmol), triethylamine (12.7 ml, 92 mmol), and 50 ml dry THF. The mixture was heated to 75 °C with a water-cooled reflux condenser for 12 h. The mixture was allowed to cool to ambient temperature,
15 was filtered through a fritted funnel, and concentrated to an orange oil. The residue was purified by silica gel chromatography (MC/MeOH/conc. NH₄OH) to give the desired product as an orange oil. MS (m/z): 318.1 (M+H)⁺. Calc'd for C₁₄H₁₈F₃N₃O₂: 317.31.

20 Step 3: 1-(2-amino-4-(trifluoromethyl)phenyl)-N,N-dimethylpiperidin-4-amine

To N,N-dimethyl-1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-4-amine (3.4 g, 11 mmol)
25 was added Pd/C (10%, 0.57 g) under nitrogen. Methanol (25 mL) was added via syringe, and H₂ gas was introduced and the mixture stirred vigorously under an atmosphere of H₂. After 96 h, the mixture was flushed with nitrogen, filtered through celite and concentrated. The residue was
30 resubjected to the reaction conditions. After 12 h, the reaction was flushed with nitrogen, filtered through celite and concentrated. The resulting solid was triturated with methanol ten times to give the title compound as a pink solid. MS (m/z): 288.2 (M+H)⁺. Calc'd for C₁₄H₂₀F₃N₃: 287.32.

35

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Example 125**Synthesis of (S)-1-(2-amino-4-(trifluoromethyl)phenyl)-N,N-dimethylpiperidin-3-amine**Step 1: (S)-N,N-dimethyl-1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-amine

10 To a light yellow solution of (S)-tert-butyl 3-aminopiperidine-1-carboxylate (0.52 g, 2.6 mmol) in 25 ml MeOH was added sodium cyanoborohydride (0.33 g, 5.2 mmol), AcOH (0.74 ml, 13 mmol), and formaldehyde (37 wt.% solution in water, 1.0 ml). After stirring approximately 12 h, the

15 reaction was quenched by the addition of 5 ml saturated aqueous sodium bicarbonate. The volatile organic solvents were removed in vacuo, and water and EtOAc was added. The organic layer was removed, and the aqueous layer was extracted twice with EtOAc. The combined organic layers were

20 dried with Na₂SO₄, filtered, and concentrated to give a yellow oil. The resulting material was treated with 4 ml 4N HCl in dioxane at 0°C. After 2 h, the solution was concentrated in vacuo to give a light yellow solid. This solid was treated with 1-Fluoro-2-nitro-4-trifluoromethyl-

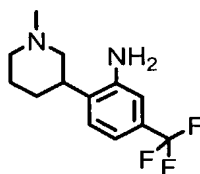
25 benzene (0.37 ml, 2.6 mmol), sodium bicarbonate (1.0 g, 13 mmol), and 5 ml dry THF. The mixture was heated to 75°C with a water-cooled reflux condenser for 12 h. The mixture was allowed to cool to ambient temperature, was filtered through a fritted funnel, and concentrated to give the desired

30 product as an orange oil. MS (m/z): 318.0 (M+H)⁺. Calc'd for C₁₄H₁₈F₃N₃O₂: 317.31.

Step 2: (S)-1-(2-amino-4-(trifluoromethyl)phenyl)-N,N-dimethylpiperidin-3-amine

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(S)-N,N-Dimethyl-1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-amine (0.82 g, 2.6 mmol) was reduced with Pd/C (10%, 0.27 g) in 10 ml methanol in a manner similar to Example 124 - Step 3 to give the title compound as an orange-red oil. MS (m/z): 288.2 (M+H)⁺. Calc'd for C₁₄H₂₀F₃N₃: 287.32.

Example 126

10 **Synthesis of 2-(1-methylpiperidin-3-yl)-5-(trifluoromethyl)benzenamine**

Step 1: 3-(2-nitro-4-(trifluoromethyl)phenyl)pyridine

A mixture of pyridin-3-ylboronic acid (0.99 g, 8.1 mmol), 2-bromo-5-(trifluoromethyl)benzenamine (1.2 ml, 8.1 mmol), tetrakis(triphenylphosphine)palladium (0.28 g, 0.24 mmol), sodium carbonate (2.0 M solution in water, 8.0 ml, 16 mmol), 4 ml ethanol, and 20 ml toluene was heated to 90 °C under nitrogen with a water-cooled reflux condenser. After 12 h, mixture was cooled to ambient temperature, and was partitioned between EtOAc and 1N NaOH. The organic layer was washed once with brine, dried with Na₂SO₄, filtered, and concentrated to give a brown oil, which was further purified by silica gel chromatography (EtOAc/hexanes) to give the desired product as a waxy orange solid. MS (m/z): 269.0 (M+H)⁺. Calc'd for C₁₂H₇F₃N₂O₂: 268.19.

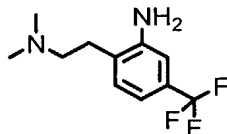
Step 2: 2-(1-methylpiperidin-3-yl)-5-(trifluoromethyl)benzenamine

30 To an orange solution of 3-(2-nitro-4-(trifluoromethyl)phenyl)pyridine (1.4 g, 5.2 mmol) in 2 ml acetone and 1 mL benzene was added iodomethane (1.0 ml, 16 mmol). The solution was allowed to stand for 5 days, and

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was concentrated in vacuo to give an orange solid. A portion of this material was treated with platinum (IV) oxide (0.11 g, 0.49 mmol) in 5 ml MeOH under an atmosphere of hydrogen for approximately 24 h. The reaction was flushed with nitrogen, filtered through celite, and concentrated. Purification by silica gel chromatography (MC/MeOH/conc. NH_4OH) provided the title compound. MS (m/z): 259.0 (M+H)⁺. Calc'd for $\text{C}_{13}\text{H}_{17}\text{F}_3\text{N}_2$: 258.28.

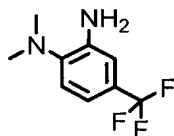
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Example 127**Synthesis of 2-(2-(dimethylamino)ethyl)-5-(trifluoromethyl)benzenamine**

15

The title compound was synthesized in a manner similar to that described in Example 58 of pending U.S. Patent Application No. 60/569,193. MS (m/z): 233.1 (M+H)⁺. Calc'd for $\text{C}_{11}\text{H}_{15}\text{F}_3\text{N}_2$: 232.25.

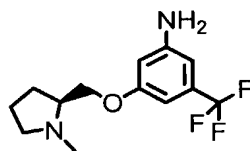
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Example 128**Synthesis of N1,N1-dimethyl-4-(trifluoromethyl)benzene-1,2-diamine**

25

The title compound was synthesized in a manner similar to Example 55 of pending U.S. Patent Application No. 60/569,193. MS (m/z): 205.1 (M+H)⁺. Calc'd for $\text{C}_9\text{H}_{11}\text{F}_3\text{N}_2$: 204.19.

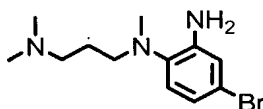
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Example 129

Synthesis of (S)-3-((1-methylpyrrolidin-2-yl)methoxy)-5-(trifluoromethyl)benzenamine

5

The title compound was synthesized by a method similar to that described in WO 2002066470 A1.

Example 130

10

Synthesis of 4-bromo-N1-(3-(dimethylamino)propyl)-N1-methylbenzene-1,2-diamine

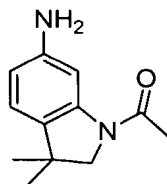
To *N*-(4-Bromo-2-nitro-phenyl)-*N*, *N'*, *N'*-trimethyl-propane-1,3-diamine (made by a method similar to that of Example 103 - Step 1) (0.54 g, 1.7 mmol) in 20 ml EtOH was added SnCl₂ (0.51 g, 2.67 mmol). The mixture was sealed and was heated to 80°C for 12 h. An additional amount of SnCl₂ (0.51 g, 2.67 mmol) was added and heating continued for 12 h. The reaction was cooled to ambient temperature, and was poured into a mixture of EtOAc and saturated aqueous sodium bicarbonate. The mixture was filtered through celite, and the organic layer was removed. The aqueous layer was extracted twice with EtOAc, and the combined organic layers were dried with Na₂SO₄, filtered, and concentrated to give a cloudy oil. This material was filtered through silica gel with 90/10/1 dichloromethane/MeOH/conc. NH₄OH and concentrated in vacuo to give the title compound as a red oil. MS (ES⁺): 285.9 (M+H)⁺. Calc'd for C₁₂H₂₀BrN₃: 286.21.

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Examples 131-141 were prepared by methods similar to the procedures described in pending U.S. Patent Application No. 60/569,193.

Example No	Structure	Example No.	Structure
131		136	
132		137	
133		138	
134		139	
135		140	
		141	

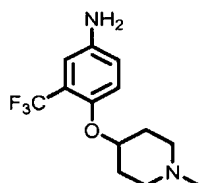
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Example 142

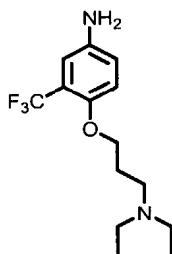
1-(6-amino-3,3-dimethylindolin-1-yl)ethanone

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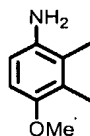
The title compound was prepared according to a procedure described in U.S. Patent Publication No. 2003/0203922.

Example 143**4-(1-methylpiperidin-4-yloxy)-3-(trifluoromethyl)benzenamine**

The title compound was synthesized in a manner similar to Example 56 of pending U.S. Patent Application No. 60/569,193.

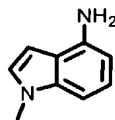
Example 144**4-(3-(diethylamino)propoxy)-3-(trifluoromethyl)benzenamine**

The title compound was synthesized in a manner similar to Example 143 above.

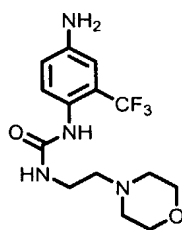
Example 145**4-methoxy-2,3-dimethylbenzenamine**

The title compound was synthesized in a manner similar to Example 143 above.

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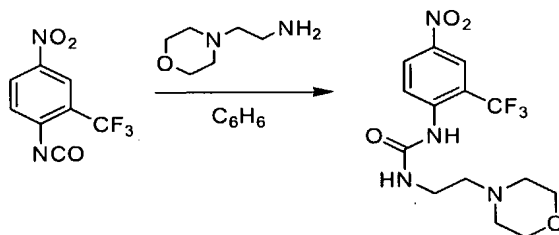
Example 146**1-methyl-1H-indol-4-amine**

The title compound was synthesized in a manner similar
 5 to Example 143 above.

Example 147

10 **1-(4-amino-2-(trifluoromethyl)phenyl)-3-(2-morpholinoethyl)urea**

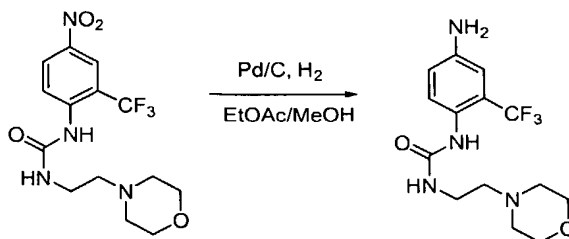
Step 1: 1-(2-morpholinoethyl)-3-(4-nitro-2-
 15 (trifluoromethyl)phenyl)urea



To a solution of 1-isocyanato-4-nitro-2-(trifluoromethyl)benzene (339 μ L, 2.21 mmol, 1.0 equiv) in benzene (3.0 mL), was added 2-morpholinoethanamine (316 mg,
 20 2.43 mmol, 1.0 equiv). The resulting precipitant was filtered and washed with hexanes to provide 1-(2-morpholinoethyl)-3-(4-nitro-2-(trifluoromethyl)phenyl)urea, which was advanced without further purification. MS (MH^+) 363; Calculated for $C_{14}H_{17}F_3N_4O_4$: 362.1

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Step 2: 1-(4-amino-2-(trifluoromethyl)phenyl)-3-(2-morpholinoethyl)urea

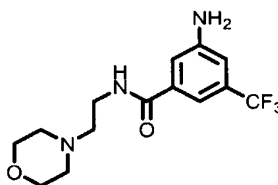


5

A mixture of 1-(2-morpholinoethyl)-3-(4-nitro-2-(trifluoromethyl)phenyl)urea (651 mg, 1.80 mmol, 1.0 equiv) and 10% Pd/C (20 mg) in EtOAc (25 mL) and MeOH (2 mL) was exposed to an atmosphere of H₂ (balloon). Upon completion of the reduction, the reaction mixture was filtered through celite and concentrated *in vacuo* to afford 1-(4-amino-2-(trifluoromethyl)phenyl)-3-(2-morpholinoethyl)urea, which was advanced without further purification. MS *m/z*: 333 (M+H⁺); Calculated for C₁₄H₁₉F₃N₄O₂: 332.2

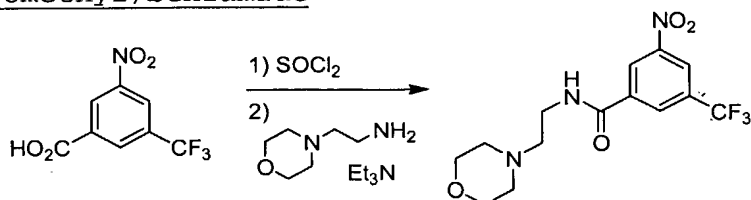
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Example 148



20 3-amino-N-(2-morpholinoethyl)-5-(trifluoromethyl)benzamide

Step 1: N-(2-morpholinoethyl)-3-nitro-5-(trifluoromethyl)benzamide



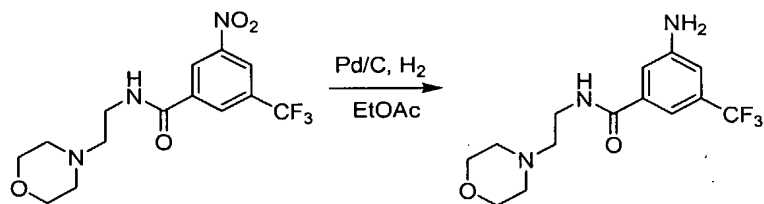
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A mixture of 3-nitro-5-(trifluoromethyl)benzoic acid (300 mg, 1.29 mmol, 1.0 equiv) and thionyl chloride (2.0 ml)

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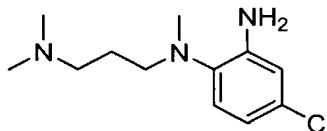
was heated at 75°C for 1h. The solvent was removed *in vacuo* and the residue taken up in CH₂Cl₂ (5.0 ml). To the solution was added 2-morpholinoethanamine (185 mg, 1.42 mmol, 1.1 equiv) and triethylamine (0.54 ml, 3.86 mmol, 3.0 equiv). After the reaction was complete, the solution was diluted with CH₂Cl₂ (ca.10 ml) and washed with water and brine. After drying with Na₂SO₄ and concentration *in vacuo*, the resulting N-(2-morpholinoethyl)-3-nitro-5-(trifluoromethyl)benzamide was advanced without further purification. MS m/z: 348 (M+H⁺); Calculated for C₁₄H₁₆F₃N₃O₄: 347.1

Step 2: 3-amino-N-(2-morpholinoethyl)-5-(trifluoromethyl)benzamide



A mixture of N-(2-morpholinoethyl)-3-nitro-5-(trifluoromethyl)benzamide (300 mg, 0.865 mmol, 1.0 equiv) and 10% Pd/C (20 mg) in EtOAc (25 ml) and MeOH (2 mL) was exposed to an atmosphere of H₂ (balloon). Upon completion of the reduction, the reaction mixture was filtered through celite and concentrated *in vacuo* to afford 3-amino-N-(2-morpholinoethyl)-5-(trifluoromethyl)benzamide, which was advanced without further purification. MS m/z: 318 (M+H⁺); Calculated for C₁₄H₁₈F₃N₃O₂: 317.1

Example 149



4-chloro-N1-(3-(dimethylamino)propyl)-N1-methylbenzene-1,2-diamine

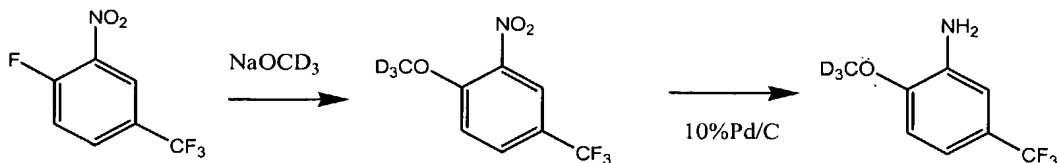
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Step 1: Preparation of 4-chloro-N-(3-(dimethylamino)propyl)-N-methyl-2-nitrobenzenamine

To 2,5-dichloronitrobenzene (3.0 g, 16 mmol) was added
 5 N1,N1,N3-trimethylpropane-1,3-diamine (2.2 g, 19 mmol). The
 mixture was stirred for 2.5 days at RT, diluted with 0.01 N
 HCl and extracted with EtOAc. The aqueous layer was made
 basic with Na₂CO₃ and extracted with EtOAc. The organic
 layer was dried over anhydrous Na₂SO₄, filtered and
 10 concentrated to yield 4-chloro-N-(3-(dimethylamino)propyl)-
 N-methyl-2-nitrobenzenamine as an orange oil. MS *m/z* = 272
 [M+H]⁺. Calc'd for C₁₂H₁₈ClN₃O₂: 271.75.

Step 2: Preparation of 4-chloro-N1-(3-(dimethylamino)propyl)-N1-methylbenzene-1,2-diamine

15 To 4-chloro-N-(3-(dimethylamino)propyl)-N-methyl-2-
 nitrobenzenamine (4.0 g, 15 mmol) in EtOH (80 ml) and water
 (10 ml) was added Raney-Ni (10 g). The mixture was stirred
 for 5 hours at RT, filtered through a pad of Celite and
 20 concentrated to yield 4-chloro-N1-(3-(dimethylamino)propyl)-
 N1-methylbenzene-1,2-diamine as a deep red oil. MS *m/z* = 242
 [M+H]⁺. Calc'd for C₁₂H₂₀ClN₃: 241.77.

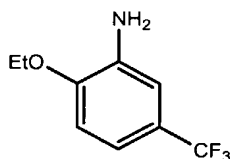
Example 150**3-amino-4-deuteromethoxy(-d₃)benzotrifluoride**

30 Step 1: To 10 g of deuterated methanol over an ice bath was
 added sodium metal until a cloudy solution formed. 4-
 Chloro-3-nitrobenzotrifluoride (2.25 g, 1.46 mL, 0.01 mol),
 was added to the solution dropwise over an ice bath. The
 reaction mixture was allowed to stir 24 hours at room

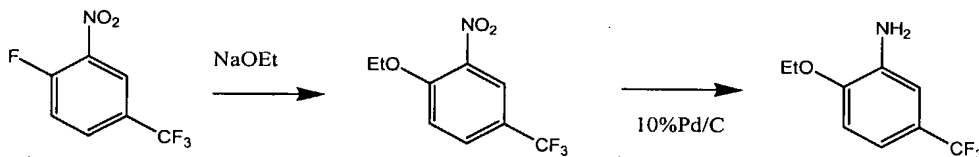
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temperature. The orange solution is brought to pH 6 (turns yellow) with acetic acid added dropwise over an ice bath.

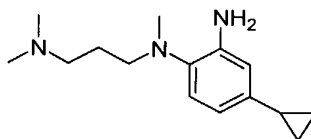
Step 2: 10% Palladium on carbon (0.05 g) was added to a reaction mixture of the nitroaniline (0.01 mol) allowed to stir at room temperature under a H₂(g) atmosphere (via balloon). The reaction mixture was then filtered through celite. The filtrate was concentrated to afford a yellow oil that was reconstituted in dichloromethane (5 ml) and purified by flash silica column using isocratic 90/10/1 : CH₂Cl₂/CH₃OH/NH₄OH. A very pale yellow solid is isolated. LC-MS(+) revealed a mass of 195 (M+H⁺); calc'd for C₈H₅D₃F₃NO: 194.17.

Example 151

15

3-amino-4-ethoxybenzotrifluoride

The title compound was prepared by a method similar to Example 150, using ethanol in place of deuteromethanol and purified by flash silica column using isocratic 90/10/1: CH₂Cl₂/CH₃OH/NH₄OH. A very pale yellow solid was isolated. LC-MS(+) revealed a mass of 206 (M+H⁺); calc'd for C₉H₁₀F₃NO: 205.18.

Example 152

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4-cyclopropyl-N1-(3-(dimethylamino)propyl)-N1-methylbenzene-1,2-diamine

5 Step 1: N-(4-Bromo-2-nitro-phenyl)-N, N',N'-trimethyl-propane-1,3-diamine

To a round bottom flask at 0°C was added 4-Bromo-1-fluoro-2-nitrobenzene (10 g, 45.46mmol) and N, N, N'-Trimethyl-propane-1,3-diamine (6.99ml, 47.73mmol). The reaction was allowed to warm to RT and stirred for 16h. The reaction was extracted into EtOAc, washed once with saturated aqueous NaHCO₃, twice with water, and then dried over Mg₂SO₄. The organic layer was filtered and concentrated to yield the title compound as a bright orange solid.

MS (M+H⁺) = 316, 318; Calc'd for C₁₂H₁₈BrN₃O₂ = 316.19.

Step 2: 4-cyclopropyl-N-(3-(dimethylamino)propyl)-N-methyl-2-nitrobenzenamine

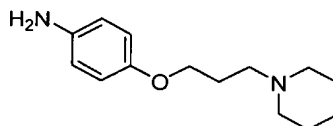
20 To a pressure vessel was added 2-cyclopropyl-4,4,5,5-tetramethyl-1,3,2-dioxaborolane (900mg, 5.36mmol), potassium phosphate (3.0g, 14.42mmol), and 0.82mL water. After stirring at RT for 15 minutes, N-(4-Bromo-2-nitro-phenyl)-N, N',N'-trimethyl-propane-1,3-diamine (Step 1, 1.30g, 4.12mmol), palladium acetate (92mg, 0.412mmol), tricyclohexylphosphine (231mg 0.824mmol), and 21 ml toluene were added. The reaction was sealed and stirred at 80°C for 19h. The reaction was then cooled to RT, quenched with EtOAc and extracted into water, washed once with brine, and then dried over Mg₂SO₄. The crude mixture was then purified by reverse phase chromatography to yield the title compound as a dark red-brown oil. MS (M+H⁺) = 278; Calc'd for C₁₅H₂₃N₃O₂ = 277.36.

35 Step 3: 4-cyclopropyl-N1-(3-(dimethylamino)propyl)-N1-methylbenzene-1,2-diamine

4-cyclopropyl-N-(3-(dimethylamino)propyl)-N-methyl-2-nitrobenzenamine (Step 2, 600mg, 2.16mmol) was dissolved in

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22mL MeOH. Palladium (115mg, 0.108mmol, 10% w/w on carbon) was added, a balloon containing hydrogen was inserted, and the reaction was stirred at RT for 18h. The solution was then filtered through a pad of Celite and concentrated, yielding the title compound as viscous red-brown oil. MS (M+H⁺) = 248; Calc'd for C₁₅H₂₅N₃ = 247.38.

Example 153**4-(3-Piperidin-1-yl-propoxy)aniline**Step 1: 1-(3-Chloropropyl)piperidine

A mixture of 1-bromo-3-chloropropane (65.6 g, 0.417 mol) and piperidine (62 ml, 0.625 mol) in anhydrous THF (200 ml) was heated to reflux for 24 h. The mixture was cooled to RT and filtered to remove solids. The organics were concentrated under in vacuo. The resultant residue was taken up in 2N HCl and washed twice with ethyl acetate. The aqueous layer was basicified with 2N NaOH to pH 14. The compound was extracted three times with ethyl acetate and the combined organics dried over anhydrous magnesium sulfate. The solution was then concentrated under reduced pressure to give the desired compound as a yellowish oil.

Step 2: 1-[3-(4-nitrophenoxy)propyl]piperidine

In a three-necked flask fitted with an overhead mechanical stirrer, a mixture of 1-(3-chloropropyl)piperidine (49.8 g, 0.308 mol), 4-nitrophenol (42.8 g, 0.308 mol) and potassium carbonate (212 g, 1.53 mol), in anhydrous DMF (200 mL) was heated to 94°C and stirred for 18 h. The mixture was cooled to room temperature, then diluted with 2 L water. The organics were taken up in ethyl acetate and washed twice with 2N sodium

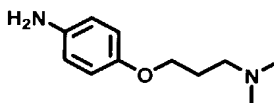
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hydroxide and then brine. The combined organics were dried over magnesium sulfate then concentrated under reduced pressure to give the title compound as a yellowish oil.

Step 3: 4-(3-Piperidin-1-ylpropoxy)aniline

5 A mixture of 1-[3-(4-nitrophenoxy)propyl]piperidine (15.5 g, 58.6 mmol) and 10% Pd/C (12.5g) in 150 mL of EtOH was placed under a balloon of H₂. The mixture was stirred for 18 h. The catalyst was removed by suction filtration and the organics concentrated to give the title compound as a
10 yellowish oil. MS (m/z) = 235.2 (M+H⁺); Calc'd for C₁₄H₂₂N₂O = 234.34.

Example 154



15

4-(3-(dimethylamino)propoxy)aniline

Step 1: 1-(3-chloropropoxy)-4-nitrobenzene

20 A solution of 4-Nitrophenol (10 g, 72 mmol) dissolved in acetonitrile (100 ml) was charged with potassium carbonate (24.9 g, 180 mmol) and 1-bromo-3-chloropropane (113.2 g, 720 mmol). The mixture was heated and stirred at reflux overnight. The reaction was cooled to room temperature, the solids filtered off and the solvent evaporated under reduced
25 pressure to give the title compound.

Step 2: 4-(3-(dimethylamino)propoxy)nitrobenzene

30 A mixture of 1-(3-chloropropoxy)-4-nitrobenzene (2 g, 9.27 mmol), potassium carbonate (7.69 g, 46.4 mmol) and acetonitrile (15 ml) was prepared and stirred in a tube. To the stirring solution dimethylamine hydrochloride (3.78 g, 46.4 mmol) was added quickly. The tube was sealed and the mixture was stirred while heating overnight at 80°C. The mixture was cooled well before opening the pressure tube, then water and dichloromethane were added and the aqueous

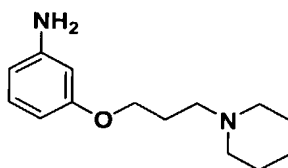
- 163 -

layer was extracted with dichloromethane. The combined organics were dried and evaporated giving the title product.

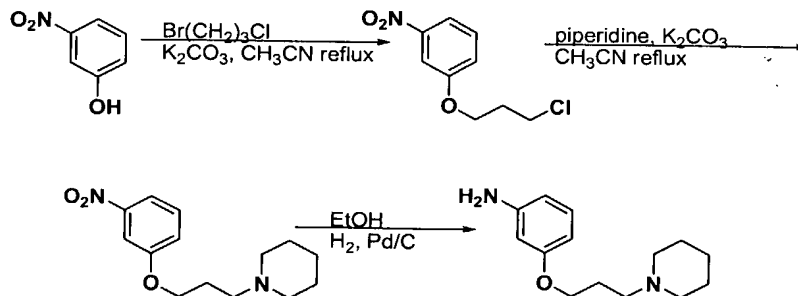
Step 3: 4-(3-(dimethylamino)propoxy)aniline

4-(3-(dimethylamino)propoxy)nitrobenzene (4.4 g, 19.6 mmol) was hydrogenated over Pd (10% on C, 0.4 g) in ethanol (50 ml) for 16 h. The catalyst was filtered off and the solvent removed under reduced pressure to afford the title compound as a brown oil. MS (m/z) = 195.3 (M+H⁺); Calc'd for C₁₁H₁₈N₂O = 194.28.

Example 155

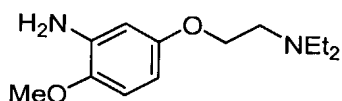


3-(3-Piperidin-1-yl-propoxy)aniline

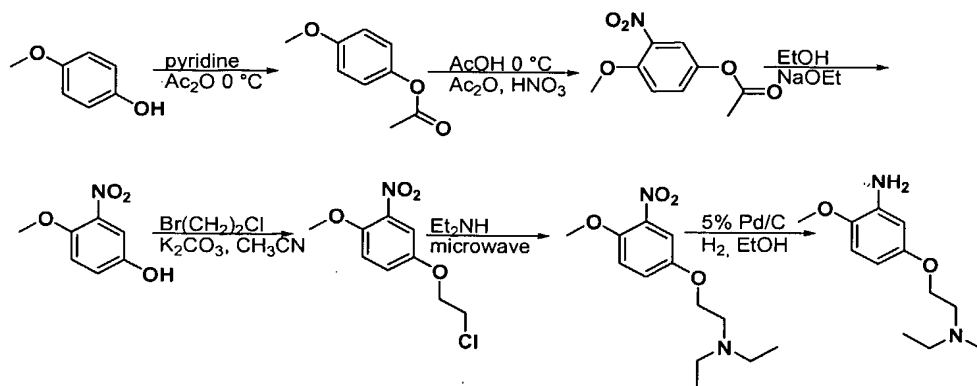


The title compound was prepared by a method similar to that described in Example 154 above, wherein 3-nitrophenol was substituted for 4-nitrophenol in Step 1 and piperidine for dimethylamine hydrochloride in Step 2. MS (m/z) = 235.2 (M+H⁺); Calc'd for C₁₄H₂₃N₂O = 234.34.

Example 156



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5-(2-(diethylamino)ethoxy)-2-methoxyaniline**5 Step 1: 4-Methoxyphenylacetate**

4-Methoxyphenol (2 g, 16 mmol) was dissolved in anhydrous pyridine (6.5 ml) and stirred while cooling at 0°C under a nitrogen atmosphere. Acetic anhydride (7.5 ml, 80 mmol) was added. The reaction was allowed to warm to room temperature, where it was stirred for 16 h. The reaction was cooled in an ice bath before quenching with ice. The solution was neutralized with saturated aqueous sodium bicarbonate solution and then extracted with ethyl acetate. The combined organic extracts were washed twice with 2M HCl, then with saturated aqueous copper sulfate solution to remove residual pyridine. The organic extract was further washed with 5M aqueous sodium hydroxide solution and brine, then dried over sodium sulfate and concentrated under reduced pressure to afford a clear oil, which crystallized to give the title compound as a white solid.

Step 2: 4-Methoxy-3-nitrophenylacetate

4-Methoxyphenylacetate (2.37g, 14.3 mmol) was dissolved in glacial acetic acid (4 ml) and cooled to 5-10 °C. A chilled mixture of glacial acetic acid (1.3 ml), fuming nitric acid (0.9 ml) and acetic anhydride (1.3 ml) was added dropwise as the temperature gradually increased to 25 °C. The reaction was stirred for 1h, then quenched with ice and diluted with water. The resulting precipitate was

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isolated by filtration, rinsed with water and dried in vacuo to afford the title compound as a fine crystalline yellow solid.

Step 3: 4-Methoxy-3-nitrophenol

- 5 4-Methoxy-3-nitrophenylacetate (2.46 g, 11.7 mmol) was dissolved in anhydrous ethanol (80 ml) and sodium ethoxide (1.19 g, 17.5 mmol) was added. The reaction was stirred at room temperature for 0.5 h. The dark red solution was acidified with 2M HCl and concentrated under reduced
10 pressure. The residue was taken up into water and extracted with dichloromethane. The combined organics were washed with 2M HCl and brine, then dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave the title compound as a yellow solid.

15 Step 4: 4-(2-chloroethoxy)-1-methoxy-2-nitrobenzene

- 4-Methoxy-3-nitrophenol (0.8 g, 4.7 mmol) was dissolved in acetonitrile (13 ml). Potassium carbonate (1.63g, 11.8 mmol) was added, followed by 1-bromo-2-chloroethane (3.93 ml, 47.2 mmol). The reaction was heated
20 and stirred at reflux for 20h. The reaction was cooled to room temperature, the solid was then filtered off and the solvent evaporated under reduced pressure to give the title compound.

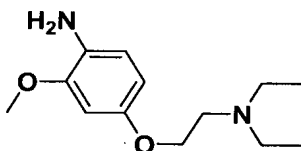
Step 5: N,N-Diethyl-2-(4-methoxy-3-nitrophenoxy)ethylamine

- 25 4-(2-chloroethoxy)-1-methoxy-2-nitrobenzene (0.15 g, 0.67 mmol) was dissolved in acetonitrile (1 ml). Excess diethylamine (1.5 ml, 17.7 mmol) was added and the reaction heated in the microwave (T= 120 °C, 40 min) to complete conversion. The reaction mixture was diluted with
30 dichloromethane, then washed with 5M sodium hydroxide and brine, then dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave the title compound as an orange oil.

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Step 6: 5-(2-(diethylamino)ethoxy)-2-methoxyphenylamine

N,N-diethyl-2-(4-methoxy-3-nitrophenoxy)ethylamine (0.29 g, 1.1 mmol) was hydrogenated over Pd (5% on C, 50% wet, 0.12 g) in ethanol (5 ml) for 16 hours. The catalyst
5 was filtered off and the solvent removed under reduced pressure to afford the title compound as a red oil. MS (*m/z*) = 239 (*M*+*H*⁺); Calc'd for C₁₃H₂₂N₂O₂ = 238.33.

Example 157

10

4-(2-(diethylamino)ethoxy)-2-methoxyanilineStep 1: 4-Fluoro-2-methoxynitrobenzene

5-Fluoro-2-nitrophenol (6 g, 38.2 mmol) was dissolved
15 in anhydrous DMF (20 ml). Potassium carbonate (5.3g, 38.2 mmol) was added, followed by iodomethane (2.28 ml, 38.2 mmol). The reaction was stirred at room temperature for 16h, then partitioned between dichloromethane and water. The organic layer was washed three times with 1M sodium
20 hydroxide and once with brine, then dried over sodium sulfate. Removal of the solvent in vacuo afforded the title compound as a yellow oil, which solidified upon standing.

Step 2: 3-Methoxy-4-nitrophenol

4-Fluoro-2-methoxynitrobenzene (4.68g, 27.4mmol) was
25 suspended in a 5M potassium hydroxide solution (50 ml) and heated to 90°C for 5h. The red solution was cooled to room temperature and acidified to pH 6 with 1M HCl. The aqueous solution was extracted three times with ethyl acetate and the combined organics were washed with brine and dried over
30 sodium sulfate. Removal of the solvent under reduced pressure, followed by purification by flash column

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chromatography (1:1 hexane/ethyl acetate) afforded the title compound as a yellow solid.

Step 3: 4-(2-chloroethoxy)-2-methoxy-1-nitrobenzene

3-Methoxy-4-nitrophenol (0.6 g, 3.6 mmol) was dissolved in acetonitrile (15 ml). Potassium carbonate (1.3 g, 9.1 mmol) was added, followed by 1-bromo-2-chloroethane (5.1 g, 35.5 mmol). The reaction was stirred in a sealed pressure tube at 80°C for 20h. The reaction was cooled to room temperature, the solid was then filtered off and the solvent evaporated under reduced pressure. The residue was then taken up into ethyl acetate and washed with 1M sodium hydroxide, brine, and then dried over sodium sulfate. Evaporation of the solvent afforded the title compound as a yellow solid.

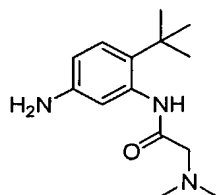
Step 4: N,N-Diethyl-2-(3-methoxy-4-nitrophenoxy)ethylamine

4-(2-Chloroethoxy)-2-methoxy-1-nitrobenzene (0.22 g, 0.9 mmol) was dissolved in acetonitrile (1 ml). Diethylamine (0.14 ml, 2.6 mmol) and potassium carbonate (0.31g, 2.2 mmol) were added and the reaction was heated in a sealed pressure tube to 80 °C for 20h. The reaction mixture was diluted with dichloromethane, then washed with 1M sodium hydroxide and brine, then dried over sodium sulfate. Evaporation of the solvent under reduced pressure gave the title compound as a brown oil.

Step 5: N,N-Diethyl -2-(4-amino-3-methoxyphenoxy)ethylamine

N,N-Diethyl-2-(3-methoxy-4-nitrophenoxy)ethylamine (140 mg, 0.5 mmol) was hydrogenated over Pd (5% on C, 50% wet, 40 mg) in ethanol (5 ml) for 16 hours. The catalyst was filtered off and the solvent removed under reduced pressure to afford the title compound as a brown oil. MS (m/z) = 239 (M+H⁺); Calc'd for C₁₃H₂₂N₂O₂ = 238.33

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Example 158**N-(5-amino-2-tert-butylphenyl)-2-dimethylaminoacetamide****Step 1: 2-tert-butyl-5-nitrobenzenamine**

5 Concentrated sulfuric acid (1 L) was cooled to -10°C with a dry ice-isopropanol bath in a 2 L 3-necked round bottom flask fitted with a mechanical stirrer and temperature probe. The 2-t-butylaniline (109 g, 730 mmol) was added, giving a clumpy solid. Once the temperature of
10 the mixture was stabilized at -10°C , the potassium nitrate (101 g, 1001 mmol) was added portion wise, as a solid, over a 4-hour period, maintaining the temperature between -20 and -5°C . Once all of the potassium nitrate was added, the reaction was left to stir overnight with gradual warming to
15 room temperature. The reaction was quenched by diluting with water and then extracting three times with EtOAc. Each of the EtOAc extracts was washed multiple times with saturated NaHCO_3 , until gas evolution ceased, and with brine. The ethyl acetate extracts were combined, dried over
20 anhydrous Na_2SO_4 , filtered and concentrated under reduced pressure giving a black oil. The oil was eluted through a 36 x 6 cm column of silica gel with EtOAc: hexanes gradient 5-50%. Solvent evaporation afforded 2-tert-butyl-5-nitrobenzenamine as a red solid.

Step 2: 2-bromo-N-(2-tert-butyl-5-nitrophenyl)acetamide

2-tert-Butyl-5-nitrobenzenamine (70 g, 359 mmol) and a catalytic amount of DMAP were dissolved into THF (1.5 L) under N_2 . Triethylamine (109 g, 1077 mmol) was added and the solution was cooled to 0°C . Bromoacetyl bromide (207 g,
30 1023 mmol) was then added and the reaction was stirred at

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room temperature for 16 hours. The reaction was then partially concentrated under reduced pressure, treated with water, and extracted three times with EtOAc. The EtOAc extracts were washed with brine, combined, dried over Na₂SO₄ and concentrated to a black oil. The oil was purified using silica chromatography, 95:5:0.5 CH₂Cl₂:MeOH:NH₄OH, giving 2-bromo-N-(2-tert-butyl-5-nitrophenyl)acetamide as a brown solid.

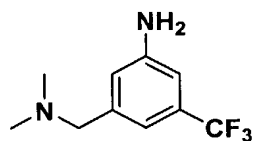
10 Step 3: N-(2-tert-butyl-5-nitrophenyl)-2-(dimethylamino)acetamide

2-Bromo-N-(2-tert-butyl-5-nitrophenyl)acetamide (80 g, 253, mmol) and potassium carbonate (70 g, 506 mmol) were combined in THF (1.75 L), and the mixture was cooled to 0 °C. N,N-Dimethylamine (40 mL of a 2 M solution in THF, 800 mmol) was then added to the mixture through an addition funnel over a 30-minute period. The mixture was then stirred at room temperature for 16 hours. The mixture was filtered and the filtrate concentrated. The crude material was purified by silica chromatography eluting with 50% EtOAc:hexanes to give N-(2-tert-butyl-5-nitrophenyl)-2-(dimethylamino)acetamide as a brown solid.

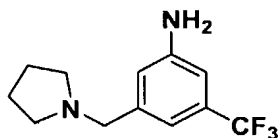
25 Step 4: N-(5-amino-2-tert-butylphenyl)-2-dimethylamino)acetamide

To a solution of N-(2-tert-butyl-5-nitrophenyl)-2-(dimethylamino)acetamide (25,8 g, 02 mmol) in 1,4-dioxane (200 mL) was added 10% Pd/C (2.5 g) as a slurry in a minimal amount of EtOH. The mixture was evacuated and purged with H₂, and stirred at room temperature for 16 hours. The reaction was then purged with N₂ and filtered through celite. The filtrate was concentrated and purified using silica chromatography, 97.5:2.5:0.25 to 95:5:0.5 CH₂Cl₂:MeOH:NH₄OH, to afford N-(5-amino-2-tert-butylphenyl)-2-dimethylamino)acetamide as a brown solid.

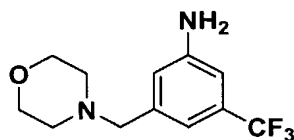
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Example 159**3-((dimethylamino)methyl)-5-(trifluoromethyl)benzenamine**

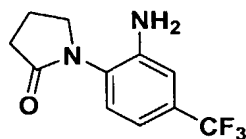
The title compound was synthesized using a procedure similar to that described in Example 95. MS m/z = 219 [M+H]⁺. Calc'd for C₁₀H₁₃F₃N₂: 218.

Example 160**3-(pyrrolidin-1-ylmethyl)-5-(trifluoromethyl)benzenamine**

The title compound was synthesized using a procedure similar to that described in Example 95. MS m/z = 245 [M+H]⁺. Calc'd for C₁₂H₁₅F₃N₂: 244.

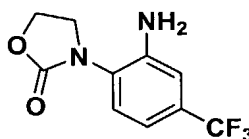
Example 161**3-(pyrrolidin-1-ylmethyl)-5-(trifluoromethyl)benzenamine**

The title compound was synthesized using a procedure similar to that described in Example 95. MS m/z = 261 [M+H]⁺. Calc'd for C₁₂H₁₅F₃N₂O: 260.

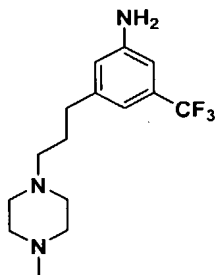
Example 162**1-(2-amino-4-(trifluoromethyl)phenyl)pyrrolidin-2-one**

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A resealable tube was charged with 2-bromo-5-(trifluoromethyl)aniline (1.00 g, 4.16 mmol), 2-pyrrolidinone (0.425 g, 5.00 mmol), N,N'-ethylene diamine (0.037 g, 0.42 mmol), potassium carbonate (1.15 g, 8.32 mmol), copper iodide (0.80 mg, 0.42 mmol) and toluene (1.0 mL). The tube was sealed and the mixture was heated at 80 °C for 24 h. The resulting mixture was partitioned between ethyl acetate and water. The organic phase was separated, dried over anhydrous sodium sulfate, filtered, and concentrated. The residue was purified via column chromatography on silica gel (gradient elution with 0-100% ethyl acetate-hexane) to afford 1-(2-amino-4-(trifluoromethyl)phenyl)pyrrolidin-2-one as a gray solid. MS m/z = 245 $[M+H]^+$. Calc'd for $C_{11}H_{11}F_3N_2O$: 244.

Example 163**3-(2-amino-4-(trifluoromethyl)phenyl)oxazolidin-2-one**

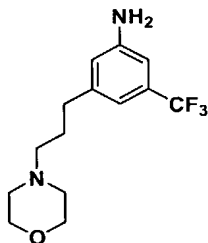
The title compound was synthesized using a procedure similar to that described in Example 162. MS m/z = 247 $[M+H]^+$. Calc'd for $C_{10}H_9F_3N_2O_2$: 246.

Example 164**3-(3-(4-methylpiperazin-1-yl)propyl)-5-(trifluoromethyl)benzenamine**

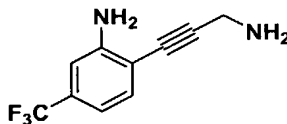
A solution of 1-allyl-4-methylpiperazine (2.12 g, 14.0 mmol) and 9-BBN (0.5 M in THF, 1.7 g, 28 mL, 14.0 mmol) was

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heated at reflux for 3 h and then cooled to RT. The solution was added to a mixture of 3-bromo-5-(trifluoromethyl)aniline (3.00 g, 12.5 mmol), potassium carbonate (8.64 g, 62.5 mmol), $\text{PdCl}_2(\text{PPh}_3)_2\text{-CH}_2\text{Cl}_2$ adduct (0.457 g, 0.6 mmol), DMF (30 mL) and water (2 mL). The mixture was heated to 75°C for 24. The mixture was concentrated, triturated with dichloromethane, and filtered. The filtrate was concentrated and the residue was purified via column chromatography on silica gel (gradient elution with 0-20% methanol-dichloromethane) to afford 3-(3-(4-methylpiperazin-1-yl)propyl)-5-(trifluoromethyl)benzenamine as a brown oil. MS m/z = 302 $[\text{M}+\text{H}]^+$. Calc'd for $\text{C}_{15}\text{H}_{22}\text{F}_3\text{N}_3$: 301.

Example 165**15 3-(3-morpholinopropyl)-5-(trifluoromethyl)benzenamine**

The title compound was synthesized using a procedure similar to that described in Example 164. MS m/z = 289 $[\text{M}+\text{H}]^+$. Calc'd for $\text{C}_{14}\text{H}_{19}\text{F}_3\text{N}_2\text{O}$: 288.

Example 166

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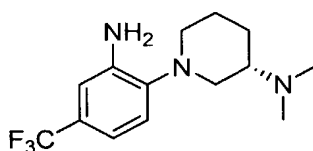
2-(3-dimethylamino-1-propynyl)-5-(trifluoromethyl)aniline

A resealable tube was charged with 2-bromo-5-(trifluoromethyl)aniline (1.00 g, 4.16 mmol), 1-dimethylamino-2-propyne (0.520 g, 6.20 mmol), $\text{PdCl}_2(\text{PPh}_3)_2$ (0.15 g, 0.21 mmol), copper iodide (0.80 mg, 0.42 mmol), diisopropylethylamine (1.0 mL) and acetonitrile (3.0 mL). The system was purged with argon, the tube sealed and the mixture stirred at room temperature for 20 h. The reaction

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mixture was filtered through celite and concentrated. The residue was purified via column chromatography on silica gel (gradient elution with 0-10% methanol-dichloromethane) to afford 2-(3-dimethylamino-1-propynyl)-5-

- 5 (trifluoromethyl)aniline as a brown oil. MS m/z = 243
[M+H]⁺. Calc'd for C₁₂H₁₃F₃N₂: 242.

Example 167

10

(S)-1-(2-amino-4-(trifluoromethyl)phenyl)-N,N-dimethylpiperidin-3-amine

- 15 Step 1: (S)-tert-butyl 1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-ylcarbamate

To a 200-mL RBF was added (s)-3-n-boc-amino piperidine (10.9 g, 54.4 mmol), Sodium bicarbonate (11.4 g, 136 mmol), THF, and 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (7.62 ml, 54.4 mmol). The yellow mixture was heated to 70°C. with a water-cooled reflux condenser. The orange mixture was allowed to stir for 14h, and was then cooled to ambient temperature, and filtered through a glass frit, rinsing with EtOAc. Concentration in vacuo afforded an orange oil, which crystallized on standing to an orange solid. The material was treated with 250mL hexanes and heated on the rotovap (no vacuum) to 60°C. Small amounts of EtOAc were added until all solid dissolved, total volume of EtOAc was approx 10mL. The solution was allowed to cool overnight, resulting in the formation of orange crystals. The liquid was decanted and the crystals rinsed twice with 50mL hexanes. The crystals were collected to give (S)-tert-butyl 1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-ylcarbamate as orange crystals. The filtrate was concentrated to an orange solid.

35 This material was treated with 150 mL hexanes and was heated

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to 65°C. Almost all of the material had dissolved. The hot liquid was decanted into a flask and allowed to cool overnight, resulting in an orange solid. The liquid was discarded, and additional crystals of (S)-tert-butyl 1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-ylcarbamate were collected. MS m/z = 390 $[M+H]^+$. Calc'd for $C_{17}H_{20}F_3N_3$: 389.

Step 2: (S)-1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-amine dihydrochloride

10 A solution of (S)-tert-butyl 1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-ylcarbamate (15.64 g, 40 mmol) was cooled to 7°C and hydrochloric acid 4.0 M dioxane (80 ml, 321 mmol) was added and the mixture allowed to warm to ambient temperature. The orange solution was allowed to stir for 14h, at which point it was concentrated in vacuo to give (S)-1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-amine dihydrochloride as a yellow solid. MS m/z = 290 $[M+H]^+$. Calc'd for $C_{12}H_{14}F_3N_3O_2$: 289.

20 Step 3: (S)-N,N-dimethyl-1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-amine

To a yellow solution of (S)-1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-amine dihydrochloride (13.39 g, 37 mmol) in 123 mL MeOH under nitrogen at 0°C was added formaldehyde (37% solution) (14 ml, 185 mmol), Acetic acid (11 ml, 185 mmol), and sodium cyanoborohydride (4.6 g, 74 mmol) in portions over 5 min. The cloudy mixture was warmed to ambient temperature. After 10 min, the reaction became quite hot and was cooled with an ice bath. After 1.5 h, the reaction was complete by LCMS. The solvent was removed in vacuo, and the flask cooled to 0°C. Water was added, and the mixture was basified with 1N NaOH, and 6N NaOH. The mixture was extracted with 1 x 200 mL EtOAc, 1 x 100 mL EtOAc, and the combined organics were dried over anhydrous Na_2SO_4 and concentrated in vacuo to give (S)-N,N-dimethyl-1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-

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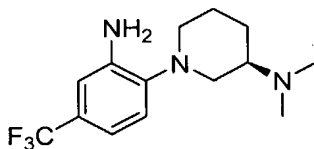
amine as an orange oil. MS m/z = 318 $[M+H]^+$. Calc'd for $C_{14}H_{18}F_3N_3O_2$: 317.

Step 4: (S)-1-(2-amino-4-(trifluoromethyl)phenyl)-N,N-dimethylpiperidin-3-amine

5 A 500mL parr pressure bottle was charged with palladium, 10wt.% on activated carbon, 50% water wet (9.1 g, 8.6 mmol) under nitrogen. (S)-N,N-dimethyl-1-(2-nitro-4-(trifluoromethyl)phenyl)piperidin-3-amine (13.6 g, 43 mmol)
10 was added as a solution in methanol via syringe, rinsing in with multiple methanol washes until the final volume was approximately 100mL. The vessel was placed in a parr shaker, and treated with 2atm H_2 and shaken overnight. The reaction was flushed with nitrogen, and filtered through a
15 pad of celite rinsing with 1.3 L of methanol and concentrated in vacuo. The oil was taken up in CH_2Cl_2 , dried over Na_2SO_4 , filtered, and concentrated in vacuo to give (S)-1-(2-amino-4-(trifluoromethyl)phenyl)-N,N-dimethylpiperidin-3-amine as a red oil. MS m/z = 288
20 $[M+H]^+$. Calc'd for $C_{14}H_{20}F_3N_3$: 287.

Example 167 was also made by a different method as described in Example 125 herein.

Example 168

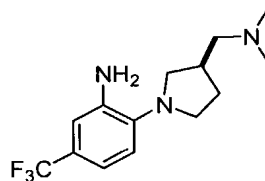


25

(R)-1-(2-amino-4-(trifluoromethyl)phenyl)-N,N-dimethylpiperidin-3-amine

The title compound was synthesized using a procedure
30 similar to that described in Example 167. MS m/z = 288
 $[M+H]^+$. Calc'd for $C_{14}H_{20}F_3N_3$: 287.

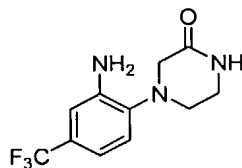
- 176 -

Example 169

5 **(R)-2-(3-((dimethylamino)methyl)pyrrolidin-1-yl)-5-(trifluoromethyl)benzenamine**

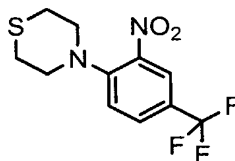
The title compound was synthesized using a procedure similar to that described in Example 167. MS m/z = 288 [M+H]⁺. Calc'd for C₁₄H₂₀F₃N₃: 287.

10

Example 170

(4-(2-amino-4-(trifluoromethyl)phenyl)piperazin-2-one

15 The title compound was synthesized using a procedure similar to that described in pending U.S. Patent Application No. 60/569,193. MS m/z = 260 [M+H]⁺. Calc'd for C₁₁H₁₂F₃N₃O: 259.

Example 171

20

Synthesis of 4-(2-nitro-4-(trifluoromethyl)phenyl)thiomorpholine

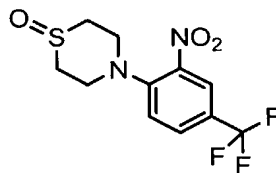
25 To a solution of 1-fluoro-2-nitro-4-(trifluoromethyl)benzene (7.00 g, 33.48 mmol) in THF (250 ml) at room temperature was added thiomorpholine (3.45 g, 33.48 mmol) and sodium bicarbonate (3.66 g, 43.52 mmol).

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The vessel was purged with nitrogen and stirred at room temperature for 48 hours. After removal of solvent under reduced pressure, the mixture was taken up in ethyl acetate and filtered. The organics were washed with water, then
5 brine and dried with magnesium sulfate. Filtration and concentration provided the title compound as a bright orange solid. MS m/z: 293.1 (M+H⁺); calc MW = 292.28.

Example 172

10

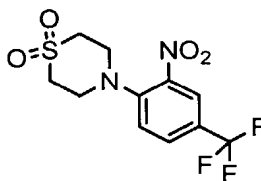
**Synthesis of the sulfoxide of 4-(2-nitro-4-(trifluoromethyl)phenyl)thiomorpholine**

15

To a solution of 4-(2-nitro-4-(trifluoromethyl)phenyl)thiomorpholine (2.0 g, 6.84 mmol) in methanol (60 ml) and water (15 ml) was added NaIO₄ (1.61 g, 7.53 mmol). The mixture was allowed to stir at room
20 temperature for 12 hours, at which time it was filtered to remove white solid precipitates. Concentration afforded the title compound as an orange solid. MS m/z: 309 (M+H⁺); calc'd MW = 308.28.

Example 173

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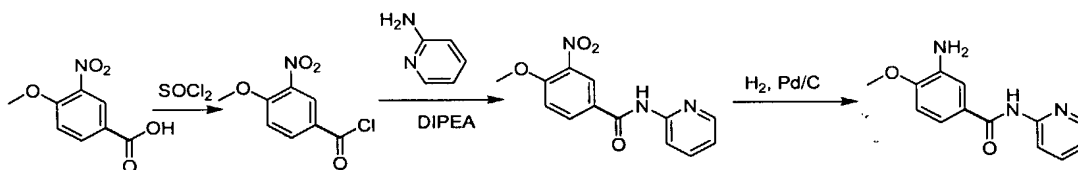
**Synthesis of the sulfone of 4-(2-nitro-4-(trifluoromethyl)phenyl)thiomorpholine**

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To a solution of the sulfoxide of 4-(2-nitro-4-(trifluoromethyl)phenyl)thiomorpholine (170 mg, 0.55 mmol) in methanol (50 ml) was added KMNO_4 (96 mg, 0.61 mmol). The reaction was stirred at room temperature for 15 minutes and then quenched by the addition of aqueous saturated sodium bisulfate (20 ml). The reaction was filtered and concentrated to provide the sulfone product. MS m/z : 325 ($M+H^+$); calc'd MW = 324.28.

The nitro groups of Examples 173-175 were reduced to the corresponding amine by conventional methods, such as be hydrogenation in the presence of a palladium catalyst. The reduction product of Example 173 was found to have a MS (m/z) = 263.1 ($M+H^+$); calc'd MW = 262.30, and the reduction product of Example 175 was found to have a MS (m/z) = 295.1 ($M+H^+$); Calc'd MW = 294.30.

Example 176**Synthesis of 3-amino-4-methoxy-N-(pyridine-3-yl)benzamide.**

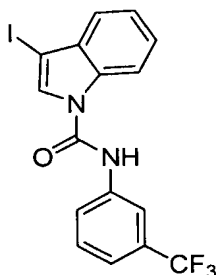
Step 1: 4-methoxy-3-nitrobenzoic acid (10.0 g, 0.051 mol), and thionyl chloride (25 g, 0.212 mol), were refluxed together for 24 hours. The reaction mixture was cooled to room temperature and concentrated. The off-white solid was carried onto the next step.

Step 2: 4-methoxy-3-nitrobenzoyl chloride (1.08g, 0.005 mol), 2-aminopyridine (0.94 g, 0.01 mol) and DIPEA (1.8 mL, 0.01 mol) were allowed to stir in dichloromethane (10mL) for 48 hours to form 4-methoxy-3-nitro-N-(pyridin-2-yl)benzamide. Intermediate was purified via silica column chromatography using 0 to 100% ethyl acetate in hexane.

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Step 3: Into a 100 mL round bottom flask was placed 4-methoxy-3-nitro-N-(pyridin-2-yl)benzamide (0.735 g, 2.69 mmol), 10% Palladium on carbon (250 mg), ethanol (50 mL), and acetic acid (10 mL) under inert atmosphere. Atmosphere then
5 exchanged with hydrogen (via balloon) and allowed to stir 24 hours at room temperature. Reaction mixture was filtered through celite, concentrated under reduced pressure, then purified via silica column chromatography using 0 to 100% ethyl acetate in hexane. MS m/z = 244 $[M+H]^+$. Calc'd for
10 $C_{13}H_{13}N_3O_2$: 243.3.

Various different B rings (R^2 groups), which are contemplated herein, may be commercially purchased or made by various methods, as represented by Examples 177-182a.

Example 177

15

Synthesis of 3-iodo-N-(3-(trifluoromethyl)phenyl)-1H-indole-1-carboxamide

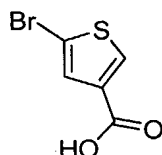
To a solution of 3-iodoindole (583 mg, 2.4 mmol)
20 (Witulski, B.; Buschmann, N.; Bergstrasser, U. *Tetrahedron* **2000**, 56, 8473-8480.) in DMF (10 mL) at 0°C was added NaH (125 mg, 3.1 mmol, 60% dispersion in mineral oil). The reaction mixture was allowed to warm to room temperature and stir for 0.5 h. Then 1-isocyanato-3-(trifluoromethyl)benzene
25 (0.38 mL, 2.64 mmol) was added and allowed to stir for an additional 0.5 h. Sat. aq. NH_4Cl (20 mL) was added and the mixture was poured onto water (50 mL). The aqueous layer was extracted with Et_2O (3 x 25 mL). The combined organics were washed with brine (10 mL), dried over anhydrous sodium

- 180 -

sulfate, filtered and concentrated under reduced pressure. The crude concentrate was purified via automated flash chromatography (silica gel, 0 to 50% EtOAc in hexanes, gradient elution) to afford 3-iodo-N-(3-(trifluoromethyl)phenyl)-1H-indole-1-carboxamide.

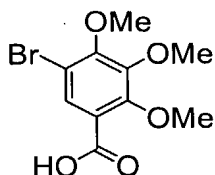
Example 178

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15

5-Bromothiophene-3-carboxylic acid was prepared by a method similar to that described in Campaigne, E. E.; Bourgeois, R. C. *J. Am. Chem. Soc.* 1954, 76, 2445-7. MS (m/z) = 206 (M-H⁺).

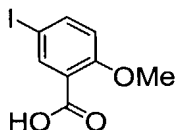
Example 179**Synthesis of 5-bromo-2,3,4-trimethoxybenzoic acid**

20

To a solution of 2,3,4-trimethoxybenzoic acid (4.7 g, 22 mmol) and NaOAc (5.5 g, 40 mmol) in 35 ml AcOH was added a solution of bromine (1.5 ml, 29 mmol) in 35 ml AcOH. The reaction became red in color, which quickly faded. The mixture was heated to 80°C for 1 h, at which point it was cooled to ambient temperature. The material was partitioned between dichloromethane and water. The organic layer was removed and the aqueous layer was extracted once with dichloromethane. The combined organic layers were dried with Na₂SO₄, filtered, and concentrated to give an oil which solidified on standing. The material was dissolved in diethyl ether and hexanes. Concentration to ½ the volume

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resulted in precipitation of a white solid. Filtration provided the title compound as a white solid. MS m/z: 293 (M+H⁺); calc'd for C₁₀H₁₁BrO₅: 291.1

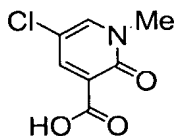
Example 180**Synthesis of 5-iodo-2-methoxybenzoic acid**Step 1. Synthesis of methyl 5-iodo-2-methoxy benzoate

To a solution of 5-iodosalicylic acid (10.0 g, 38 mmol) in 189 ml acetone was added potassium carbonate (23 g, 169 mmol). The mixture was cooled to 0 °C and dimethyl sulfate (7.7 ml, 80 mmol) was added. The mixture was heated to reflux overnight and was cooled to ambient temperature and concentrated under reduced pressure. The residue was partitioned between EtOAc and water, and the aqueous layer was extracted three times with EtOAc. The combined organic layers were dried with Na₂SO₄, filtered, and concentrated to give a white solid. This material was heated with hexanes and allowed to stand for 60 h, resulting in the formation of crystals. Filtration provided the title compound as white needles. MS (ES⁺): 292.9 (M+H)⁺. Calc'd for C₉H₉IO₃: 292.07.

Step 2. Synthesis of 5-iodo-2-methoxybenzoic acid

A mixture of methyl 5-iodo-2-methoxy benzoate (6.0 g, 21 mmol) and 23 ml each MeOH and 1N NaOH was heated with a water-cooled reflux condensor to 90 °C for 2 h. The reaction was cooled to ambient temperature, 100 mL water was added, and the solution adjusted to pH 1 with 6N HCl. A thick white precipitate formed which was collected by filtration to give the title compound as a white solid. MS (m/z): 278.9 (M+H)⁺. Calc'd for C₈H₇IO₃: 278.04.

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Example 181**Synthesis of 5-chloro-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid**Step 1. Synthesis of methyl 5-chloro-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate

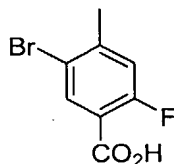
10 To a suspension of 5-chloro-2-hydroxynicotinic acid (2.0 g, 12 mmol) and cesium carbonate (8.2 g, 26 mmol) in 50 mL DMF was added MeI (1.6 ml, 26 mmol). The reaction was allowed to stir for approximately 12 h. The cloudy yellow mixture was added to EtOAc/water. The organic layer was removed and the aqueous layer was extracted three times with EtOAc. The combined organic layers were washed once with water and brine, dried with Na₂SO₄, filtered, and concentrated to give an orange-yellow solid. The material was partitioned between 1N HCl and EtOAc. The organic layer was washed twice with 1N HCl, dried with Na₂SO₄, filtered, and concentrated to give the desired product as an orange solid. MS (m/z): 202.0 (M+H)⁺. Calc'd for C₈H₈ClNO₃: 201.61.

Step 2. Synthesis of 5-chloro-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylic acid

25 A mixture of methyl-5-chloro-1-methyl-2-oxo-1,2-dihydropyridine-3-carboxylate (0.36 g, 1.8 mmol) and 2.0 mL each MeOH and 1N NaOH was heated in a sealed vial to 80 °C for 1 h. The reaction was cooled to ambient temperature, and the methanol was removed by a stream of nitrogen. Water (2 ml) was added and the solution was adjusted to pH 1 with 6N HCl. A thick white precipitate formed which was partitioned between water and dichloromethane. The organic layer was removed and the aqueous layer was extracted twice with 35 dichloromethane. The combined organic layers were dried with

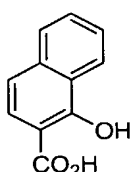
- 183 -

Na₂SO₄, filtered, and concentrated to give an orange-yellow solid. The material was partitioned between 1N HCl and EtOAc. The organic layer was washed twice with 1N HCl, dried with Na₂SO₄, filtered, and concentrated to give the desired product as a light orange solid. MS (m/z): 188.0 (M+H)⁺. Calc'd for C₇H₆ClNO₃: 187.58.

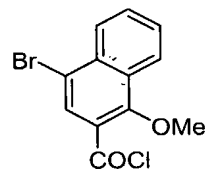
Example 182

10

5-bromo-2-fluoro-4-methylbenzoic acid was prepared by a method described in PCT Patent Publication WO 2003/032972.

Example 182a

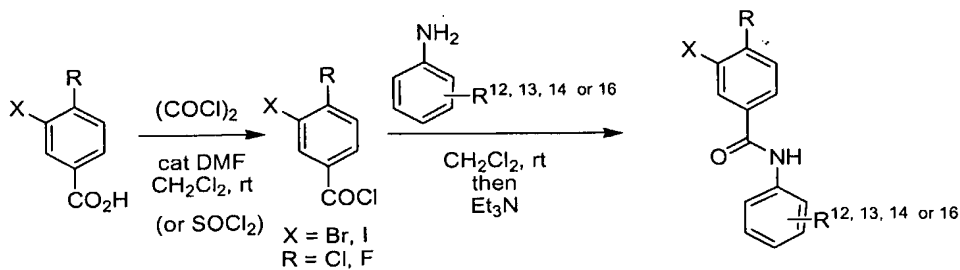
1.) Br₂, AcOH, RT
 2.) Dimethyl Sulfate, K₂CO₃, Acetone, Reflux
 3a.) NaOH, MeOH, 70°C
 3b.) HCl, RT
 4.) (COCl)₂, DMF, CH₂Cl₂, RT



15

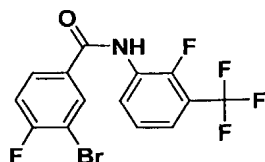
The title compound was prepared according to a literature procedure published in *J. Med. Chem.* **2001**, *44*, 1815.

Various different A-B linked ring intermediates (substituted R² groups), which are contemplated herein, may be made by various methods, such as with A-B amide linked rings, as represented by Examples 183-191.

Example 183

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Synthesis of 3-bromo-4-fluoro-N-(2-fluoro-3-(trifluoromethyl)phenyl)benzamide



5

Step 1: 3-Bromo-4-fluorobenzoyl chloride

Oxalyl chloride (1.739 g, 1.20 ml, 13.7 mmol) was added dropwise to a solution of 3-bromo-4-fluorobenzoic acid (0.600 mg, 2.74 mmol) and dichloromethane (9 ml). N,N-Dimethylformamide (1 drop) was added and the colorless solution stirred at rt for 1 h. The solution was concentrated to afford 3-bromo-4-fluorobenzoyl chloride an off-white solid which was used directed without purification.

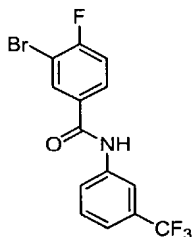
15

Step 2: 3-Bromo-4-fluoro-N-(2-fluoro-3-(trifluoromethyl)phenyl)benzamide

2-Fluoro-3-(trifluoromethyl)aniline (0.515 g, 0.37 mL, 2.88 mmol) was added to a solution of 3-bromo-4-fluorobenzoyl chloride (0.650 g, 2.74 mmol) in dichloromethane (5 ml), and the mixture stirred at room temperature for 30 min. Triethylamine (0.360 g, 0.50 ml, 3.56 mmol) was added and the solution stirred at room temperature for 1 h. The reaction mixture was partitioned between dichloromethane and saturated aqueous sodium bicarbonate solution. The aqueous phase was separated and extracted with dichloromethane. The combined organic phases were washed with water, brine, dried over anhydrous sodium sulfate, filtered, and concentrated to afford a light yellow solid. Trituration with dichloromethane and filtering afforded 3-bromo-4-fluoro-N-(2-fluoro-3-(trifluoromethyl)phenyl)benzamide as a white solid. MS (M-H⁺) 377.9; Calculated for C₁₄H₇BrF₅NO: 379.

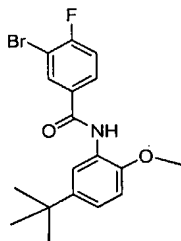
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Example 184

5 **Synthesis of 3-Bromo-4-fluoro-N-(3-(trifluoromethyl)phenyl)benzamide**

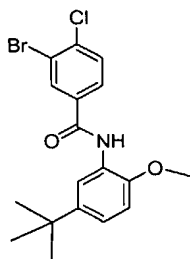
3-Bromo-4-fluoro-N-(3-(trifluoromethyl)phenyl)benzamide was synthesized from 3-trifluoromethylaniline and 3-bromo-4-fluorobenzoyl chloride
10 according to the procedure described in Example 183, affording the title compound as a white solid. MS (M-H⁺) 360.0; Calculated for C₁₄H₈BrF₄NO: 361.

Example 185

15 **Synthesis of 3-Bromo-N-(5-tert-butyl-2-methoxyphenyl)-4-fluorobenzamide**

3-Bromo-N-(5-tert-butyl-2-methoxyphenyl)-4-fluorobenzamide was synthesized from 5-tert-butyl-o-anisidine and 3-bromo-4-fluorobenzoyl chloride according to
20 the procedure described in Example 183, affording the title compound as an off-white solid. MS (M+H⁺) 380.0; Calculated for C₁₈H₁₉BrFNO₂: 379.

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Example 186**Synthesis of 3-Bromo-N-(5-tert-butyl-2-methoxyphenyl)-4-chlorobenzamide**

5

Step 1: 3-Bromo-4-chlorobenzoyl chloride

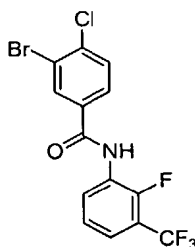
3-Bromo-4-chlorobenzoyl chloride was prepared from 3-bromo-4-chlorobenzoic acid according to the procedure described in Example 183 for the synthesis of 3-bromo-4-fluorobenzoyl chloride.

10

Step 2: 3-Bromo-N-(5-tert-butyl-2-methoxyphenyl)-4-chlorobenzamide

3-Bromo-N-(5-tert-butyl-2-methoxyphenyl)-4-chlorobenzamide was synthesized from 5-tert-butyl-o-anisidine and 3-bromo-4-chlorobenzoyl chloride according to the procedure described in Example 183, step 2. 3-Bromo-N-(5-tert-butyl-2-methoxyphenyl)-4-chlorobenzamide was obtained as an off-white solid. MS (M-H⁺) 394.0; Calculated for C₁₈H₁₉BrClNO₂: 395.

20

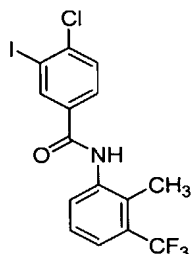
Example 187**Synthesis of 3-Bromo-4-chloro-N-(2-fluoro-3-(trifluoromethyl)phenyl)benzamide**

25

3-Bromo-4-chloro-N-(2-fluoro-3-(trifluoromethyl)phenyl)benzamide was synthesized from 2-

- 187 -

fluoro-3-(trifluoromethyl)aniline and 3-bromo-4-chlorobenzoyl chloride according to the procedure described in Example 183. 3-Bromo-4-chloro-N-(2-fluoro-3-(trifluoromethyl)phenyl)benzamide was obtained as a red-orange solid. MS (M-H⁺) 393.9; Calc'd for C₁₄H₇BrClF₄NO: 395.

Example 188

10 **Synthesis of 4-Chloro-3-iodo-N-(2-methyl-3-(trifluoromethyl)phenyl)benzamide**

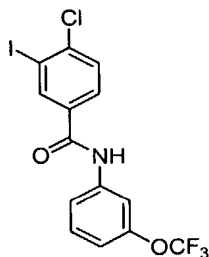
Step 1: 4-Chloro-3-iodobenzoylchloride

15 4-Chloro-3-iodobenzoylchloride was prepared from 4-chloro-3-iodobenzoic acid according to the procedure described in Example 183 for the synthesis of 3-bromo-4-fluorobenzoyl chloride.

Step 2: 4-Chloro-3-iodo-N-(2-methyl-3-(trifluoromethyl)phenyl)benzamide

20 4-Chloro-3-iodo-N-(2-methyl-3-(trifluoromethyl)phenyl)benzamide was synthesized from 2-methyl-3-(trifluoromethyl)aniline and 4-chloro-3-iodobenzoyl chloride according to the procedure described in Example 183. 4-Chloro-3-iodo-N-(2-methyl-3-(trifluoromethyl)phenyl)benzamide was obtained as a white solid. MS (M-H⁺) 437.8; Calculated for C₁₅H₁₀ClF₃INO: 439.

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Example 189
Synthesis of 4-Chloro-3-iodo-N-(3-(trifluoromethoxy)phenyl)benzamide

5

4-Chloro-3-iodo-N-(3-(trifluoromethoxy)phenyl)benzamide was synthesized from 3-(trifluoromethoxy)aniline and 4-chloro-3-iodobenzoylchloride according to the procedure described in Example 183, affording the title compound as a white solid. MS (M-H⁺) 439.8; Calculated for C₁₄H₈ClF₃INO₂: 441.

10

The following A-B amide linked ring intermediates, Examples 190-270, were made by methods similar to that described in Example 183.

15

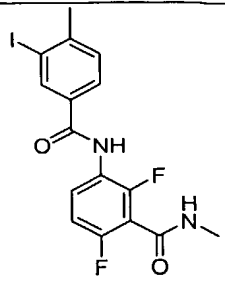
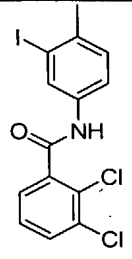
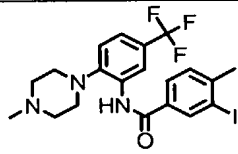
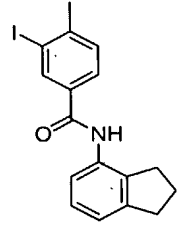
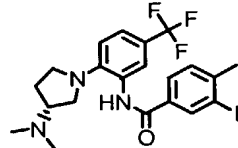
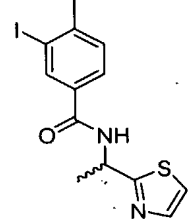
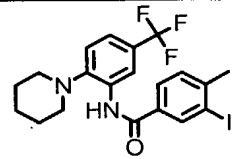
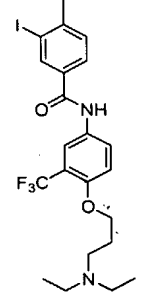
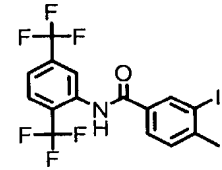
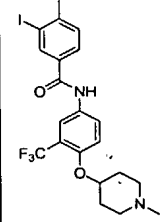
Example No.	Structure	Example No.	Structure
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191		234	

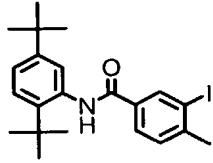
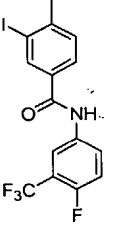
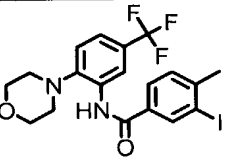
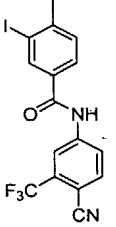
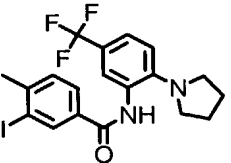
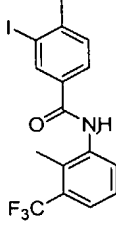
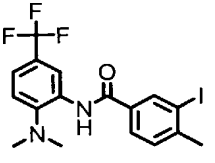
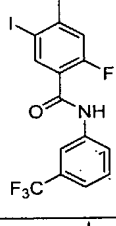
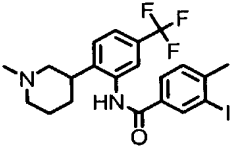
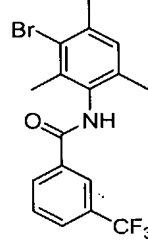
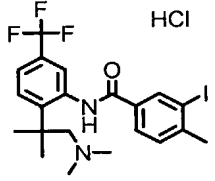
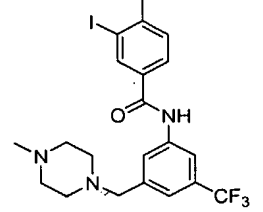
Example No.	Structure	Example No.	Structure
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194		237	
195		238	
196		239	

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Example No.	Structure	Example No.	Structure
197		240	
198		241	
199		242	
200		243	
201		244	

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Example No.	Structure	Example No.	Structure
202		245	
203		246	
204		247	
205		248	
206		249	

Example No.	Structure	Example No.	Structure
207		250	
208		251	
209		252	
210		253	
211		254	
212	 HCl	255	

Example No.	Structure	Example No.	Structure
213		256	
214		257	
215		258	
216		259	
217		260	
218		261	
219		262	

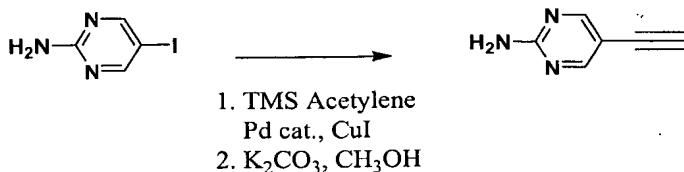
Example No.	Structure	Example No.	Structure
220		263	
221		264	
222		265	
223		266	
224		267	
225		268	

Example No.	Structure	Example No.	Structure
226		269	
227		270	
228			
229			
230			
231			
232			

Various different alkyne-substituted heteroaryl C rings (pyridines, pyrimidines, quinolines, quinazolines, imidazolo-pyridines, and the like), which are contemplated

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herein, may be made by various methods, as represented by Examples 271-275.

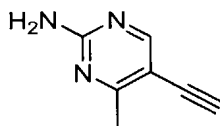
Example 271

5

Synthesis of 2-amino-5-ethynylpyrimidine

Into a 1L round bottom flask was placed the 2-amino-5-iodopyrimidine (8.0 g, 36.2 mmol), acetonitrile (300mL), triethylamine (30mL), TMS acetylene (7.68g, 78.2 mmol), palladium dichloro-bis-triphenylphosphine (1.26g, 1.8 mmol), and copper(I) iodide (0.342g, 1.8 mmol). The vessel was filled with argon gas and allowed to stir at room temperature for 3 hours. The solvent was evaporated and the crude was taken up in methanol (400mL). Then excess potassium carbonate (10eq) was added, and the mixture was stirred at room temperature for 1.5 hours. Activated charcoal was added and the mixture was filtered through celite. The filtrate was concentrated under reduced pressure to afford a tan solid, which was added to a solution of 10% methanol in water (200mL). The resulting precipitate was isolated by filtration, dried in a vacuum oven to constant mass and afforded the title compound as a tan solid. MS *m/z* = 120 [M+H]⁺. Calc'd for C₆H₅N₃: 119.

25

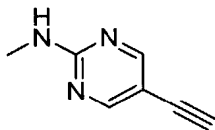
Example 272**Synthesis of 5-ethynyl-4-methylpyrimidin-2-amine**

The title compound was prepared from 5-iodo-4-methylpyrimidin-2-amine (prepared according to the method described in Sakamoto, T.; Kondo, Y.; Yamanaka, H.

30

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Synthesis, 1984, 3, 252-4) in a manner similar to that described in Example 271 above. MS (m/z): 236 ($M+H^+$)

Example 273**5 5-ethynyl-N-methylpyrimidin-2-amine**Step 1: 5-bromo-N-methylpyrimidin-2-amine

A mixture of 2-chloro-5-bromopyrimidine (2.5 g, 13 mmol), methylamine hydrochloride (7.9 g, 116 mmol), and diisopropylethylamine (18 mL, 103 mmol) in 43 mL
10 acetonitrile was heated in a sealed vessel for 16 h. The reaction was partitioned between EtOAc and water. The organic layer was washed once with brine, dried over anhydrous sodium sulfate, filtered, and concentrated to give 5-bromo-N-methylpyrimidin-2-amine. MS m/z = 188 [$M+H$]⁺.
15 Calc'd for $C_5H_6BrN_3$: 187.

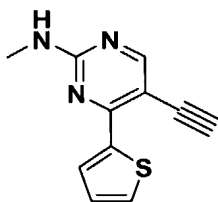
Step 2: N-methyl-5-(2-(trimethylsilyl)ethynyl)pyrimidin-2-amine

A 100 mL round bottom flask was charged with palladium(bisbenzonitrile)dichloride (0.23 g, 0.61 mmol),
20 trit-butylphosphonium tetrafluoroborate (0.35 g, 1.2 mmol) and copper (I) iodide (0.11 g, 0.61 mmol) under argon. 20 mL dioxane was added, followed by diisopropylethylamine (2.6 mL, 18 mmol), 5-bromo-N-methylpyrimidin-2-amine (2.3 g, 12 mmol), and trimethylsilyl acetylene (3.4 mL, 24 mmol). The
25 reaction was allowed to stir overnight. The cloudy brown mixture was diluted with EtOAc and filtered through a pad of silica gel and concentrated in vacuo to give a brown solid. This was further purified by silica gel chromatography, eluting with 0-50% EtOAc/dichloromethane to give N-methyl-5-(2-(trimethylsilyl)ethynyl)pyrimidin-2-amine as a yellow
30 solid. MS m/z = 206 [$M+H$]⁺. Calc'd for $C_{10}H_{15}N_3Si$: 205.

Step 3: 5-ethynyl-N-methylpyrimidin-2-amine

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To a slurry of N-methyl-5-(2-(trimethylsilyl)ethynyl)pyrimidin-2-amine (2.4 g, 12 mmol) in 60 mL methanol was added potassium carbonate (4.8 g, 35 mmol). The cloudy mixture was allowed to stir rapidly for 4 h. The mixture was then concentrated to a small volume and partitioned between water and dichloromethane. The aqueous layer was extracted 5x with dichloromethane and 2x with EtOAc. The combined organic layers were dried over anhydrous sodium sulfate, filtered, and concentrated in vacuo to give N-methyl-5-(2-(trimethylsilyl)ethynyl)pyrimidin-2-amine as a brown solid. MS m/z = 134 $[M+H]^+$. Calc'd for $C_7H_7N_3$: 133.

Example 274**5-ethynyl-N-methyl-4-(thiophen-2-yl)pyrimidin-2-amine****Step 1: 5-bromo-2-chloro-4-(thiophen-2-yl)pyrimidine**

A solution of thiophene (3.3 g, 39 mmol) in THF (100 mL) was cooled to -78°C . n-Butyllithium (2.5 M in hexane, 24 mL, 59 mmol) was added and the mixture stirred at -78°C for 1 h. 2-Chloro-5-bromopyrimidine (7.5 g, 39 mmol) was added and the mixture stirred at -78°C for 1 h. DDQ (17.7 g, 78 mmol) was added with stirring, followed by the addition of methanol (5 mL). The mixture stirred for 1 h and was then warmed to 0°C and then to RT. The reaction mixture was poured into 0.5 M sodium ascorbate (aq) solution (100 mL), and allowed to stir for 1 h. The mixture was treated with saturated aqueous potassium carbonate solution (50 mL), and extracted with ethyl acetate. The combined organic layers were dried over anhydrous sodium sulfate, filtered and concentrated. The residue was purified via column chromatography on silica gel (eluting with 100% dichloromethane) to afford 5-bromo-2-chloro-4-(thiophen-2-

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yl)pyrimidine as a yellow solid. MS m/z = 276 $[M+H]^+$. Calc'd for $C_8H_4BrClN_2S$: 275.

Step 2: 5-bromo-N-methyl-4-(thiophen-2-yl)pyrimidin-2-amine

A 16 by 100 mm vial was charged with 5-bromo-2-chloro-
5 4-(thiophen-2-yl)pyrimidine (1.00 g, 3.6 mmol), THF (4 mL),
triethylamine (1.5 ml, 11 mmol), and methylamine
hydrochloride (0.49 g, 7.3 mmol), and water (0.4 mL). The
vial was capped and heated to 85°C with stirring for 20
hours. The reaction was cooled to room temperature and
10 concentrated. The residue was purified via column
chromatography on silica gel (gradient elution with 0 to 4%
methanol in dichloromethane) to afford 5-bromo-N-methyl-4-
(thiophen-2-yl)pyrimidin-2-amine. MS m/z = 271 $[M+H]^+$.
Calc'd for $C_9H_8BrN_3S$: 270.

15 Step 3: N-methyl-4-(thiophen-2-yl)-5-(2-
(trimethylsilyl)ethynyl)pyrimidin-2-amine

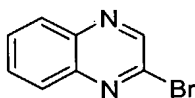
A 75 mL thick wall glass tube with a teflon screw cap
was charged with 5-bromo-N-methyl-4-(thiophen-2-
20 yl)pyrimidin-2-amine (0.995 g, 3.68 mmol), acetonitrile (9
mL), triethylamine (3.00 ml, 3.68 mmol),
dichlorobis(triphenyl)phosphine palladium(II) (0.259 g, 0.368
mmol), copper(I) iodide (0.0351 g, 0.184 mmol), and
ethynyltrimethylsilane (0.362 g, 3.68 mmol). The tube was
25 capped and heated to 90°C for 2 hours. The reaction mixture
was cooled to room temperature and concentrated. The residue
was purified via column chromatography on silica gel
(gradient elution with 0-100% ethyl acetate-hexane) to
afford N-methyl-4-(thiophen-2-yl)-5-(2-
30 (trimethylsilyl)ethynyl)pyrimidin-2-amine. MS m/z = 288
 $[M+H]^+$. Calc'd for $C_{14}H_{17}N_3SSi$: 287.

Step 4: 5-ethynyl-N-methyl-4-(thiophen-2-yl)pyrimidin-2-
amine

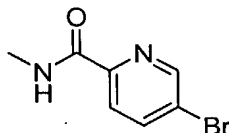
35 A 25 mL round bottom flask was charged with N-methyl-
4-(thiophen-2-yl)-5-(2-(trimethylsilyl)ethynyl)pyrimidin-2-

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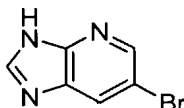
amine (0.518 g, 1.80 mmol), methanol (20 mL), and potassium carbonate (0.747 g, 5.41 mmol), and the reaction mixture stirred at room temperature for 24 hours. The reaction mixture was concentrated and the residue was purified via column chromatography on silica gel (gradient elution with 0-100% ethyl acetate-hexane) to 5-ethynyl-N-methyl-4-(thiophen-2-yl)pyrimidin-2-amine. MS m/z = 216 $[M+H]^+$. Calc'd for $C_{11}H_9N_3S$: 215.

Example 275

2-Bromoquinoxaline was prepared in a manner similar to that described in Kato, Y.; Okada, S.; Tomimoto, K.; Mase, *Tetrahedron Let.* 2001, 42, 4849-4851. MS (m/z): 210 ($M+H^+$)

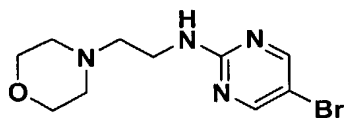
Example 276

5-Bromo-N-methylpicolinamide was prepared in a manner similar to that described in Markevitch, D. Y.; Rapt, M.; Hecker, S. J.; Renau, T. E. *Synthetic Commun.* 2003, 33, 3285-3289. MS (m/z): 217 ($M+H^+$)

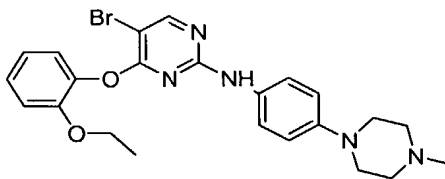
Example 277

6-Bromo-3H-imidazo[4,5-b]pyridine was prepared in a manner similar to that described in Yutilov, Y. M.; Lopatinskaya, K. Y.; Smolyar, N. N.; Korol, I. V. *Russian Journal of Organic Chemistry* 2003, 39, 280-281. MS (m/z): 199 ($M+H^+$)

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Example 278**5-bromo-N-(2-morpholinoethyl)pyrimidin-2-amine**

A resealable tube was charged with a solution of 2-chloro-5-bromopyrimidine (1.00 g, 5.17 mmol), N-(2-aminoethyl)morpholine (0.808 g, 6.20 mmol), diisopropylethylamine (0.801 g, 1.1 mL, 6.20 mmol), and THF (40 mL). The mixture was heated at 85°C for 20 h. The reaction mixture was concentrated and then purified via column chromatography on silica gel (gradient elution with 0-100% (90:10:1, dichloromethane/methanol/ammonium hydroxide)-dichloromethane) to afford 5-bromo-N-(2-morpholinoethyl)pyrimidin-2-amine as a light yellow solid. MS m/z = 288 $[M+H]^+$. Calc'd for $C_{10}H_{15}BrN_4O$: 287.

Example 278a**5-bromo-4-(2-ethoxyphenoxy)-N-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-amine**Step 1. 5-bromo-2-chloro-4-(2-ethoxyphenoxy)pyrimidine.

To a suspension of NaH (0.42 g 60% in mineral oil, 10.5 mmol) in DMF (8.0 mL) was slowly added 2-ethoxyphenol (1.34 g, 9.7 mmol) in MeCN (4.0 mL) at 0 °C under N_2 . After the addition, the reaction mixture was allowed to warm up to room temperature for 0.5 hour. 5-bromo-2,4-dichloropyrimidine (2.0 g, 8.8 mmol) in MeCN (16.0 mL) was slowly added and then the resulting reaction mixture was stirred at room temperature for 24 hour. EtOAc (120 mL) was added and washed with NaOH (30 mL, 0.5N) and brine (25x2 mL). The organic layer was dried with $MgSO_4$, and concentrated under reduced pressure. The residue was

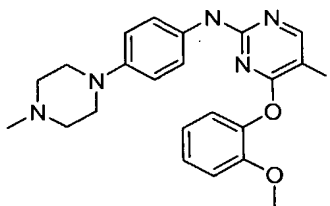
- 202 -

purified by silica gel chromatography (10% to 30% EtOAc in Hexanes, gradient elution) to provide the 5-bromo-2-chloro-4-(2-ethoxyphenoxy)pyrimidine. MS m/z = 330 $[M+1]^+$. Calc'd for: $C_{12}H_{10}BrClN_2O_2$: 329

5 Step 2. 5-bromo-4-(2-ethoxyphenoxy)-N-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-amine

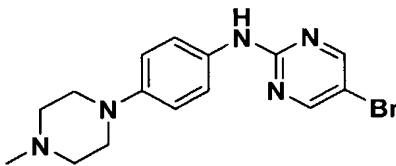
To a solution of 5-bromo-2-chloro-4-(2-ethoxy)pyrimidine (0.8 g, 2.4 mmol) and 4-(2-(pyrrolidin-1-yl)ethoxy)benzenamine (0.51 g, 2.7 mmol) in 1,4-dioxane (5.0 mL) was added trifluoroacetic acid (0.1 mL). The resulting reaction mixture was stirred at 90° C overnight. The reaction mixture was allowed to cool to room temperature, diluted with CH_2Cl_2 (200 mL) and washed with sat. aq. $NaHCO_3$ (20x2 mL) and brine (20x3 mL). The organic layer was dried with $MgSO_4$, and concentrated under reduced pressure. The residue was purified by silica gel chromatography (10% to 50% EtOAc in Hexanes, gradient elution) to get the 5-bromo-4-(2-ethoxyphenoxy)-N-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-amine. MS m/z = 485 $[M+1]^+$. Calc'd for: $C_{23}H_{26}BrN_5O_2$: 484

Example 278b



The compound above, 5-iodo-4-(2-methoxyphenoxy)-N-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-amine, was prepared by a method similar to that described in Example 278a. MS m/z = 517 $[M+H]^+$; Calc'd for: $C_{22}H_{24}IN_5O_2$: 517.36

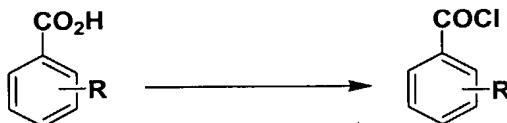
Example 278c



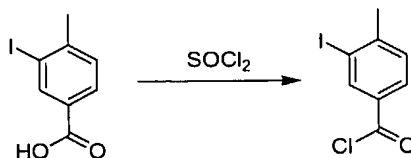
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5-bromo-N-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-amine

A resealable tube was charged with 2-chloro-5-bromopyrimidine (1.00 g, 5.21 mmol), 4-(N-methylpiperazine)aniline (1.20 g, 6.25 mmol), trifluoroacetic acid (1.78 g, 1.20 mL, 15.6 mmol), and isopropanol (50 mL). The tube was sealed and the mixture stirred at 100°C for 20 h. The reaction mixture was concentrated and the residue was purified via column chromatography on silica gel (gradient elution with 0-100% (90:10:1, dichloromethane/methanol/ammonium hydroxide)-dichloromethane) to afford 5-bromo-N-(4-(4-methylpiperazin-1-yl)phenyl)pyrimidin-2-amine. MS m/z = 348, 350 $[M+H]^+$. Calc'd for $C_{15}H_{18}BrN_5$: 348.

General Synthesis of Acid Chlorides

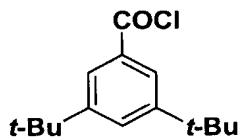
While persons of ordinary skill in the art readily appreciate how to make an acid chloride, the following Examples 279 and 280 represent methods utilized in making representative compounds of Formulas I - III.

Example 279**3-iodo-4-methylbenzoyl acid chloride**

Into a 100 mL round bottom flask is placed 3-iodo-4-methyl benzoic acid (10 g, 38.175 mmol) and thionyl chloride (25 mL, 344 mmol). The reaction was allowed to stir at reflux for 2 hours. The reaction was cooled to room temperature and concentrated under reduced pressure. The

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concentrate was placed under high vacuum for about 24hr and afforded the title acid chloride as a light yellow solid.

Example 280**5 3,5-ditert-butyl benzoyl chloride**

Oxalyl chloride (0.542 g, 0.37 ml, 4.27 mmol) was added dropwise to a solution of 3,5-di-tert-butylbenzoic acid (0.200 g, 0.853 mmol) and dichloromethane (4 ml). N,N-Dimethylformamide (1 drop) was added and the colorless
10 solution stirred at RT for 3 h. The solution was concentrated to afford 3,5-di-tert-butylbenzoyl chloride as a yellow oil.

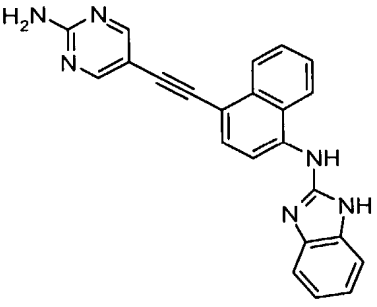
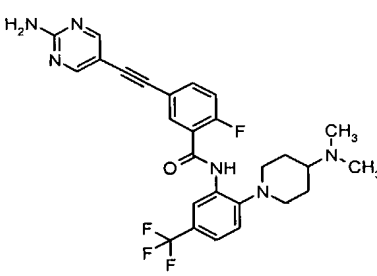
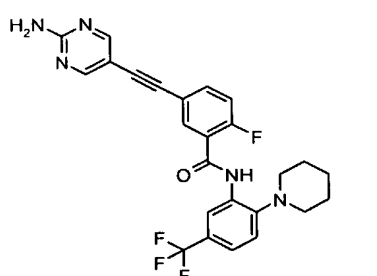
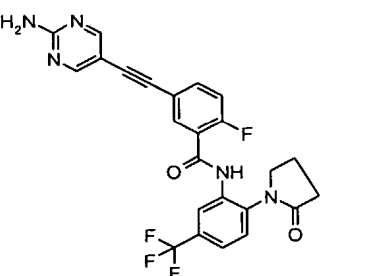
The following acid chlorides were prepared according to the methods described in Example 280 above.

15 1-methyl-1H-indole-2-carbonyl chloride, 2-chloro-3-(trifluoromethyl)benzoyl chloride, 4-chloro-3-(trifluoromethyl)benzoyl chloride, 2-chloro-3-methylbenzoyl chloride, and 2-chloro-3-fluorobenzoyl chloride.

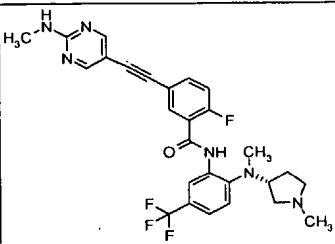
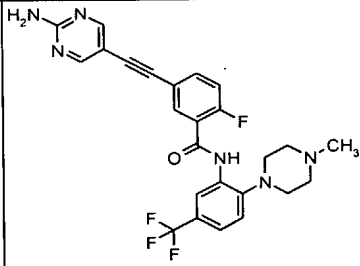
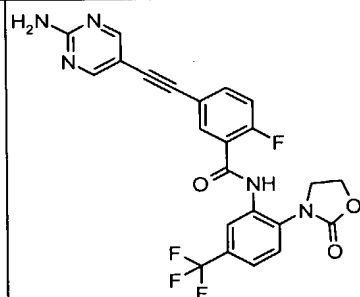
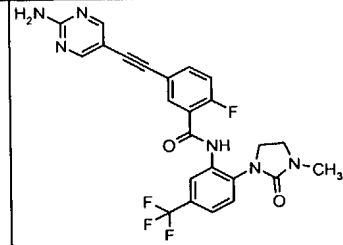
The following Examples 281-351, made using many of the
20 building blocks described above, should assist in understanding the present invention and should not be construed as limiting the scope of the invention.

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Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
281		5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-(methoxy)-1-methyl-3-(trifluoromethyl)phenyl)-2-(methoxy)benzamide	524.544	525	A1
282		N-(4-((2-amino-5-pyrimidinyl)ethynyl)phenyl)-3-(trifluoromethyl)benzamide	382.344	383	B1
283		N-(4-((2-amino-5-pyrimidinyl)ethynyl)phenyl)-1H-benzimidazol-2-amine	326.362	327	C2
284		5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3S)-3-(dimethylamino)-1-piperidyl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide	526.535	527	A1

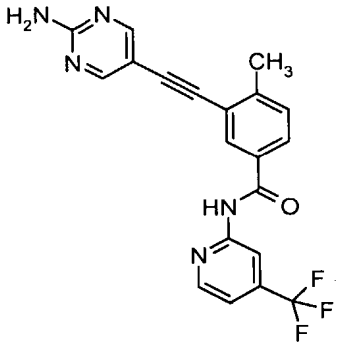
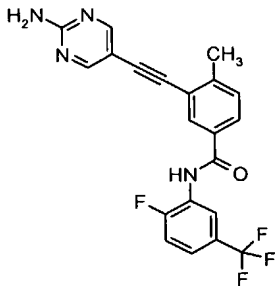
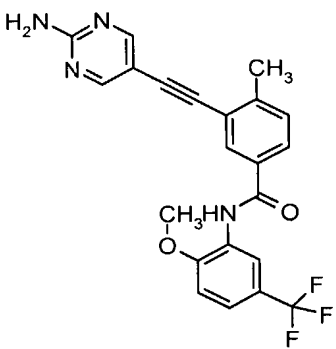
Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
285		N-(4-((2-amino-5-pyrimidinyl)ethynyl)-1-naphthalenyl)-1H-benzimidazol-2-amine	376.421	377	C2
286		5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-(4-(dimethylamino)-1-piperidinyl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide	526.535	527	A1
287		5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(1-piperidinyl)-5-(trifluoromethyl)phenyl)benzamide	483.467	484	A1
288		5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(2-oxo-1-pyrrolidinyl)-5-(trifluoromethyl)phenyl)benzamide	483.423	484	A1

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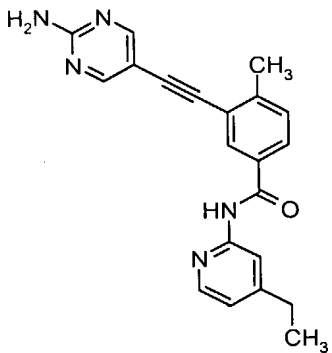
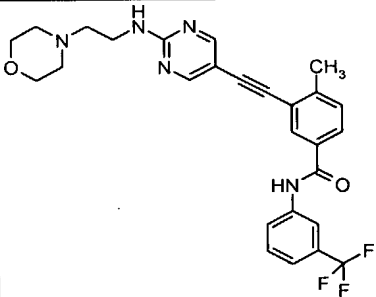
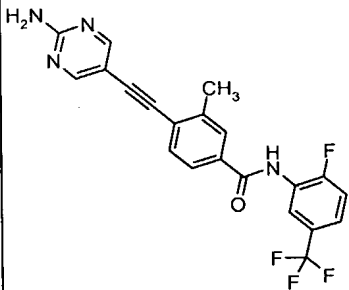
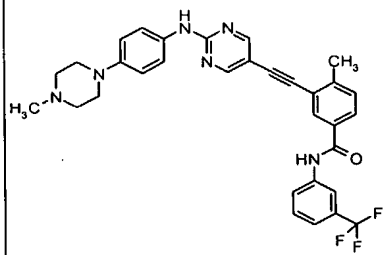
Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
289		2-fluoro-5-((2-(methylamino)-5-pyrimidinyl)ethynyl)-N-(2-(methyl((3R)-1-methyl-3-pyrrolidinyl)amino)-5-(trifluoromethyl)phenyl)benzamide	526.535	527	A1
290		5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(4-methyl-1-piperazinyl)-5-(trifluoromethyl)phenyl)benzamide	498.482	499	A1
291		5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(2-oxo-1,3-oxazolidin-3-yl)-5-(trifluoromethyl)phenyl)benzamide	485.396	486	A1
292		5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(3-methyl-2-oxo-1-imidazolidinyl)-5-(trifluoromethyl)phenyl)benzamide	498.438	499	A1

Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
293		5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3R)-3-(dimethylamino)-1-piperidinyl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide	526.535	527	A1
294		5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(3-oxo-1-piperazinyl)-5-(trifluoromethyl)phenyl)benzamide	498.438	499	A1
295		5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3R)-3-((dimethylamino)methyl)-1-pyrrolidinyl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide	526.535	527	A1
296		3-((2-amino-5-pyrimidinyl)ethynyl)-N-(4-((2-(dimethylamino)ethyl)oxy)phenyl)-4-methylbenzamide	415.495	416	A1

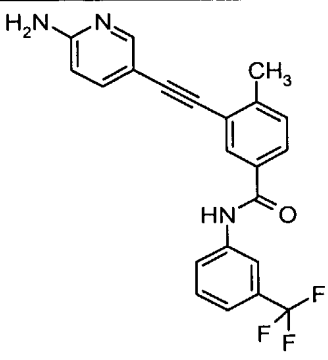
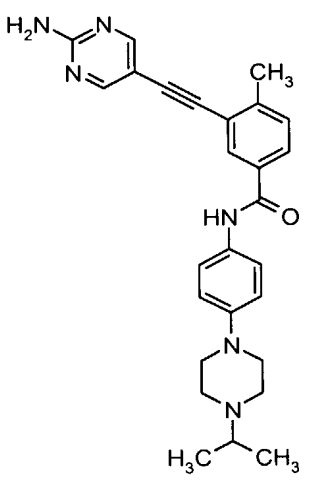
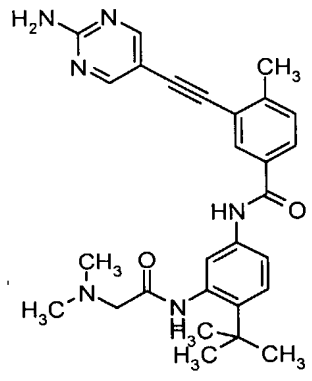
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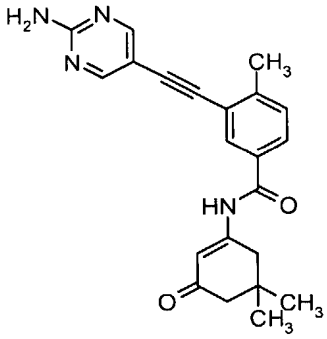
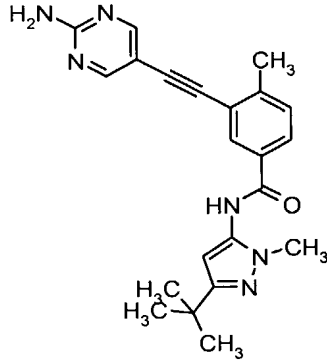
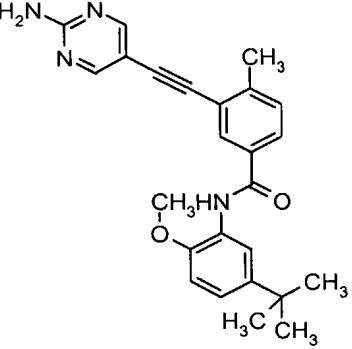
Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
297		3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(4-(trifluoromethyl)-2-pyridinyl)benzamide	397.359	398	A1
298		3-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-fluoro-5-(trifluoromethyl)phenyl)-4-methylbenzamide	414.361	415	A1
299		3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(2-(methyloxy)-5-(trifluoromethyl)phenyl)benzamide	426.396	427	A1

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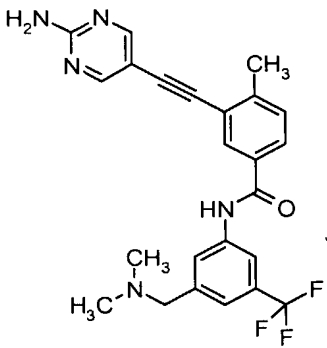
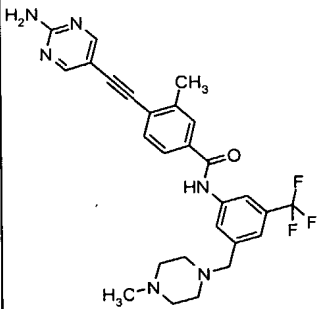
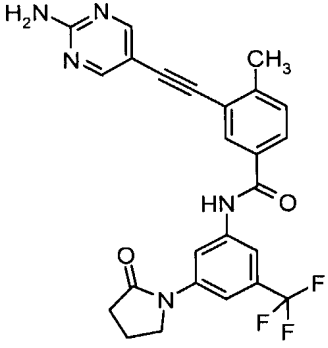
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300		3-((2-amino-5-pyrimidinyl)ethynyl)-N-(4-ethyl-2-pyridinyl)-4-methylbenzamide	357.415	358	A1
301		4-methyl-3-((2-((2-(4-morpholinyl)ethyl)amino)-5-pyrimidinyl)ethynyl)-N-(3-(trifluoromethyl)phenyl)benzamide	509.529	510	D1
302		4-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-fluoro-5-(trifluoromethyl)phenyl)-3-methylbenzamide	414.361	415	A1
303		4-methyl-3-((2-((4-(4-methyl-1-piperazinyl)phenyl)amino)-5-pyrimidinyl)ethynyl)-N-(3-(trifluoromethyl)phenyl)benzamide	570.616	571	D1

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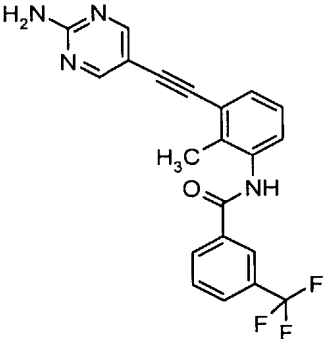
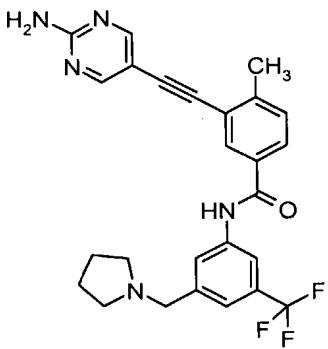
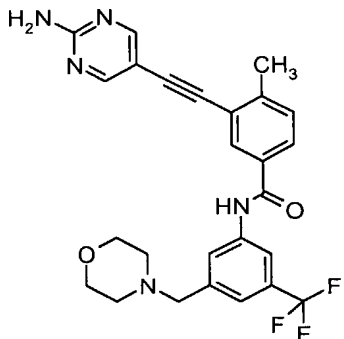
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304		3-((6-amino-3-pyridinyl)ethynyl)-4-methyl-N-(3-(trifluoromethyl)phenyl)benzamide	395.382	396	D1
305		3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(4-(4-(1-methylethyl)-1-piperazinyl)phenyl)benzamide	454.575	455	A1
306		3-((2-amino-5-pyrimidinyl)ethynyl)-N-(4-(1,1-dimethylethyl)-3-((N,N-dimethylglycyl)amino)phenyl)-4-methylbenzamide	484.601	485	A1

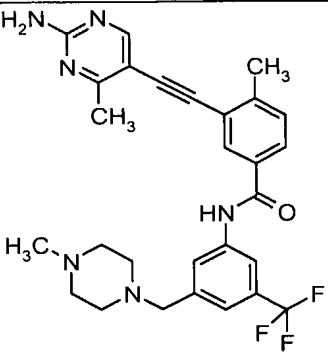
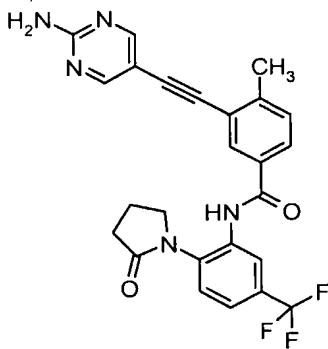
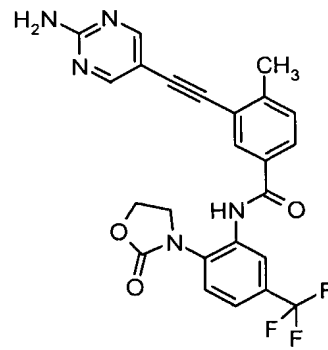
Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
307		3-((2-amino-5-pyrimidinyl)ethynyl)-N-(5,5-dimethyl-3-oxo-1-cyclohexen-1-yl)-4-methylbenzamide	374.442	375	A1
308		3-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-(1,1-dimethylethyl)-1-methyl-1H-pyrazol-5-yl)-4-methylbenzamide	388.473	389	A1
309		3-((2-amino-5-pyrimidinyl)ethynyl)-N-(5-(1,1-dimethylethyl)-2-(methoxy)phenyl)-4-methylbenzamide	414.506	415	A1

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Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
310		3-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-((dimethylamino)methyl)-5-(trifluoromethyl)phenyl)-4-methylbenzamide	453.466	454	A1
311		4-((2-amino-5-pyrimidinyl)ethynyl)-3-methyl-N-(3-((4-methyl-1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)benzamide	508.545	509	A1
312		3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-(2-oxo-1-pyrrolidinyl)-5-(trifluoromethyl)phenyl)benzamide	479.46	480	A1

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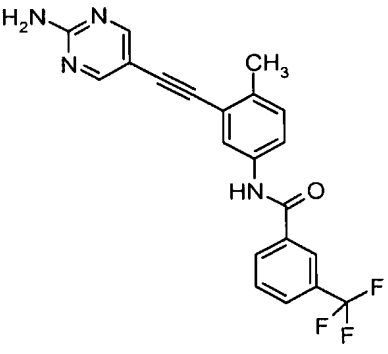
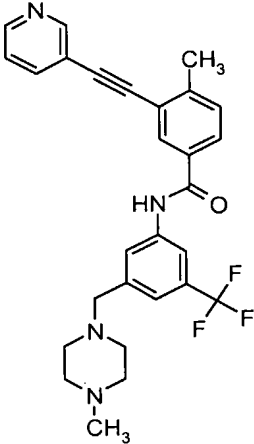
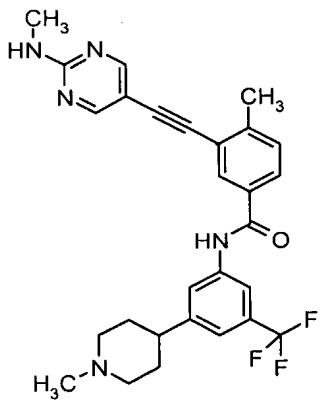
Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
313		N-(3-((2-amino-5-pyrimidinyl)ethynyl)-2-methylphenyl)-3-(trifluoromethyl)benzamide	396.371	397	A1
314		3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-(1-pyrrolidinylmethyl)-5-(trifluoromethyl)phenyl)benzamide	479.504	480	A1
315		3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-(4-morpholinylmethyl)-5-(trifluoromethyl)phenyl)benzamide	495.503	496	A1

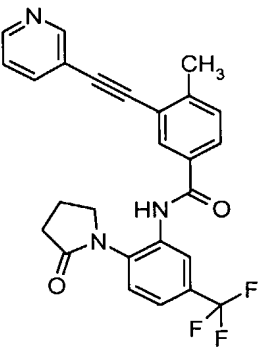
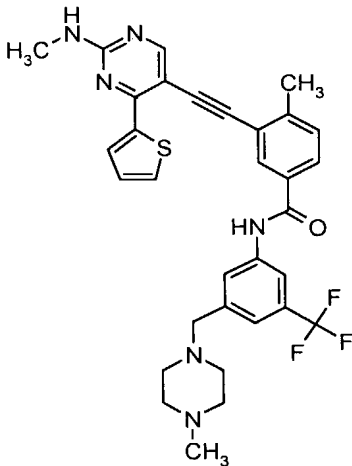
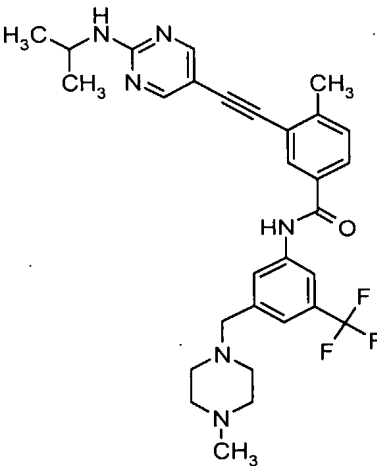
Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
316		3-((2-amino-4-methyl-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-((4-methyl-1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)benzamide	522.572	523	A1
317		3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(2-(2-oxo-1-pyrrolidinyl)-5-(trifluoromethyl)phenyl)benzamide	479.46	480	A1
318		3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(2-(2-oxo-1,3-oxazolidin-3-yl)-5-(trifluoromethyl)phenyl)benzamide	481.432	482	A1

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Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
319		3-((2-amino-5-pyrimidinyl)ethynyl)-N-(4-cyano-2-methylbenzamide)	354.372	355	A1
320		3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-(3-(4-morpholinyl)propyl)-5-(trifluoromethyl)phenyl)benzamide	523.556	524	A1
321		4-methyl-3-((2-(methylamino)-5-pyrimidinyl)ethynyl)-N-(3-((4-methyl-1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)benzamide	522.572	523	A1

Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
322		3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-(3-(4-methyl-1-piperazinyl)propyl)-5-(trifluoromethyl)phenyl)benzamide	536.599	537	A1
323		3-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-(3-(dimethylamino)-1-propyn-1-yl)-5-(trifluoromethyl)phenyl)-4-methylbenzamide	477.488	478	A1
324		3-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-(3-(dimethylamino)-1-propyn-1-yl)-5-(trifluoromethyl)phenyl)-4-methylbenzamide	477.488	478	A1

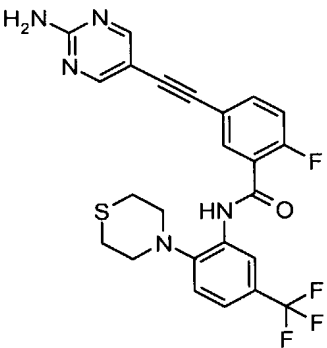
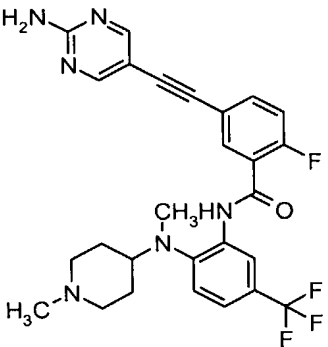
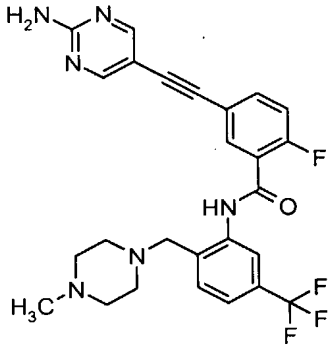
Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
325		N-(3-((2-amino-5-pyrimidinyl)ethynyl)-4-methylphenyl)-3-(trifluoromethyl)benzamide	396.371	397	A1
326		4-methyl-N-(3-((4-methyl-1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)-3-(3-pyridinylethynyl)benzamide	492.542	493	A1
327		4-methyl-3-((2-(methylamino)-5-pyrimidinyl)ethynyl)-N-(3-(1-methyl-4-piperidinyl)-5-(trifluoromethyl)phenyl)benzamide	507.557	508	A1

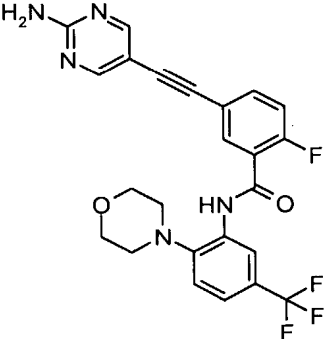
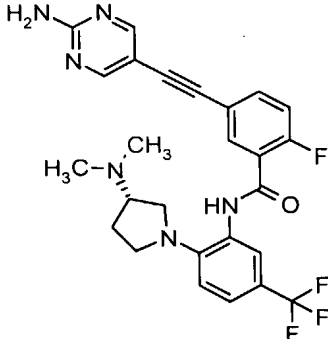
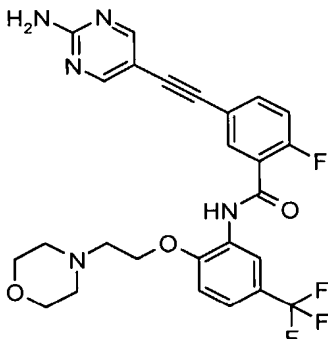
Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
328		4-methyl-N-(2-(2-oxo-1-pyrrolidinyl)-5-(trifluoromethyl)phenyl)-3-(3-pyridinylethynyl)benzamide	463.457	464	A1
329		4-methyl-3-((2-(methylamino)-4-(2-thienyl)-5-pyrimidinyl)ethynyl)-N-(3-((4-methyl-1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)benzamide	604.698	605	A1
330		4-methyl-3-((2-((1-methylethyl)amino)-5-pyrimidinyl)ethynyl)-N-(3-((4-methyl-1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)benzamide	550.626	551	A1

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Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
331		4-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-(methoxy)-1-methyl-3-pyrrolidinylamino)-5-(trifluoromethyl)phenyl)-1-(methoxy)-2-naphthalenecarboxamide	574.604	575	A1
332		4-methyl-3-((4-((2-(methoxy)phenyl)oxy)-2-((4-(4-methyl-1-piperazinyl)phenyl)amino)-5-pyrimidinyl)ethynyl)-N-(3-(trifluoromethyl)phenyl)benzamide	692.739	693	D1
333		N-(3-methyl-4-((4-((2-(methoxy)phenyl)oxy)-2-((4-(4-methyl-1-piperazinyl)phenyl)amino)-5-pyrimidinyl)ethynyl)phenyl)-N'-(3-(trifluoromethyl)phenyl)urea	707.753	708	D1
334		5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-(3,3-dimethyl-2-oxo-1-azetidinyl)-5-(trifluoromethyl)phenyl)-2-(methoxy)benzamide	509.486	510	A1

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Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
335		5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(4-thiomorpholinyl)-5-(trifluoromethyl)phenyl)benzamide	501.506	502	A1
336		5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(methyl(1-methyl-4-piperidinyl)amino)-5-(trifluoromethyl)phenyl)benzamide	526.535	527	A1
337		5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-((4-methyl-1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)benzamide	512.509	513	A1

Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
338		5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(4-morpholinyl)-5-(trifluoromethyl)phenyl)benzamide	485.439	486	A1
339		5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3S)-3-(dimethylamino)-1-pyrrolidinyl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide	512.509	513	A1
340		5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-((2-(4-morpholinyl)ethoxy)-5-(trifluoromethyl)phenyl)benzamide	529.492	530	A1

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Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
341		5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-((1S,4R)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-5-(trifluoromethyl)phenylbenzamide	510.493	511	A1
342		5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-((2-(1-pyrrolidinyl)ethyl)oxy)-5-(trifluoromethyl)phenyl)benzamide	513.493	514	A1
343		5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-(((3S)-1-ethyl-3-pyrrolidinyl)oxy)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide	513.495	514	A1

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Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
344		5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-(((3S)-1-ethyl-3-piperidinyl)oxy)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide	527.52	528	A1
345		N-(2-((3S)-3-(dimethylamino)-1-piperidinyl)-5-(trifluoromethyl)phenyl)-2-fluoro-5-((2-(methylamino)-5-pyrimidinyl)ethynyl)benzamide	540.562	541	A1
346		5-((2-amino-4-methyl-5-pyrimidinyl)ethynyl)-N-(2-((3S)-3-(dimethylamino)-1-piperidinyl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide	540.562	541	A1

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Ex. No.	Structure	Compound Name	MW	MS: M+H	Method
347		N-cyclopropyl-4-methyl-3-((2-((2-(4-morpholinyl)ethyl)amino)-5-pyrimidinyl)ethynyl)benzamide	405.499	406	A1
348		N-(4-((2-((4-(4-methyl-1-piperazinyl)phenyl)amino)-5-pyrimidinyl)ethynyl)phenyl)-1H-benzimidazol-2-amine	500.607	501	C2
349		N-(4-((2-((4-(4-methyl-1-piperazinyl)phenyl)amino)-5-pyrimidinyl)ethynyl)phenyl)-3-(trifluoromethyl)benzamide	556.589	557	B1
350		4-((2-((4-(4-methyl-1-piperazinyl)phenyl)amino)-5-pyrimidinyl)ethynyl)-N-(3-(trifluoromethyl)phenyl)benzamide	556.589	557	A1
351		N-(4-((2-amino-5-pyrimidinyl)ethynyl)phenyl)-2-(phenylamino)benzamide	405.459	406	B1

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BIOLOGICAL EVALUATION

The following assays can be employed to determine the degree of activity of a compound as a protein kinase inhibitor. Compounds described herein have been tested in one or more of these assays, and have shown activity. Representative compounds of the invention were tested and found to exhibit IC_{50} values of 25 μ M or less in any one of the described assays, thereby demonstrating and confirming the utility of the compounds of the invention as protein kinase inhibitors and in the prophylaxis and treatment of immune diseases, proliferative disorders, angiogenic diseases, etc.

TIE-2- HOMOGENOUS TIME RESOLVED FLOURESCENT (HTRF) KINASE ASSAY

IC_{50} 's for the inhibition of the Tie-2 kinase enzyme for individual compounds were measured using an HTRF assay, utilizing the following procedure:

In a 96 well plate (available from Costar Co.) was placed 1 μ L of each test and standard compound per well in 100% DMSO having a 25 μ M final compound concentration (3-fold, 10 point dilution). To each well was added 20 μ L of a reaction mix formed from Tie-2 (4.0 μ L; of a 10 mM stock solution available from Gibco), 0.05% BSA (0.1 μ L; from a 10% stock solution available from Sigma-Aldrich Co.), 0.002 mM of BLC HER-2 KKK (Biotinylated Long chain peptide; 0.04 μ L; from a 0.002 mM stock solution), 0.01 mM concentration of ATP (0.02 μ L; commercially available from Sigma-Aldrich Co.) and the remaining solution was water (15.84 μ L) to make to a total volume of 20 μ L/well.

The reaction was initiated in each well by adding 20 μ L per well of an enzyme preparation consisting of a 50 mM concentration of Hepes (1.0 μ L; from a 1000 mM stock solution commercially available from Gibco Co.), 0.05% concentration of BSA (0.1 μ L), 4 mM of DTT (0.08 μ L; from a

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1000 mM stock solution available from Sigma-Aldrich Co.), a
2.4 x 10⁻⁷ concentration of Tie-2 (0.02 uL, from a 4 mM
concentration stock), with the remaining volume being water
(18.8 uL) to dilute the enzyme preparation to a total volume
5 of 20 uL. The plate was incubated for about 90 minutes at
RT. After incubation, a 160 uL of a filtered detection
mixture, prepared from 0.001 mg/ml of SA-APC (0.0765 uL;
available as a 2.09 mg/ml stock solution from Gibco),
0.03125 nM concentration of Eu-Ab (0.1597 uL; available in a
10 31.3 nM stock solution from Gibco), with the remaining
volume being Detection buffer (159.73 uL), was added to each
well to stop the reaction therein. The plate was then
allowed to equilibrate for about 3 hr and read on a Ruby
Star fluorescent reader (available from BMG Technologies,
15 Inc.) using a 4 parameter fit using activity base to
calculate the corresponding IC₅₀'s for the test and standard
compounds in each well. The following exemplary compounds
were found to have IC₅₀'s for the inhibition of Tie-2 as
measured by the HTRF assay of less than or equal to 10 uM:
20 Examples 1-44, 46-64, 66-67, 69-77, 79 and 81-92.

TIE-2 CELL-BASED DELFIA ASSAY

Day 1 - Plate Preparation

25 Three 175ml flasks of EAHY926 cells were obtained from
the University of N. Carolina. All cells were trypsinized
(i.e., washed with 20 mL of PBS followed by 3 mL of trypsin-
EDTA obtained from Gibco Co., cat. no. 25300-054, for 5 min
at RT), then cultured in a growth medium solution containing
30 DMEM (High glucose, Gibco Co., cat. no. 1965-092), 10% FBS
serum (Gibco Co., cat. no. 10099-141) and P/S (Penicillin-
Streptomycin-Glutamine; Gibco Co., cat. no. 10378-016)
culture media. The cells were counted using a Z2® coulter®
counter. The cells were plated in four 24-well tissue

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culture plates (Costar Co., cat. no. 353047) to initially contain 4×10^5 cells/ml per well, and then loaded to 500 uL volume having a final cell density of 2×10^5 cells/well. The cells were incubated for 5 or more hours at 37 °C under 5% CO₂. The DMEM + 10% serum + P/S culture media was removed and the cells washed twice with 500 uL of PBS (without Ca+ and Mg++; Gibco Co., cat. no. 14190-136) at RT. 500 uL of 0.5% FBS + F12 (F12 nutrient mixture; Gibco Co., cat. no. 11765-054) was added to each well and the cells were incubated at 37 °C overnight (about 15 hr).

100ug of anti-hTie2 antibody (R & D Systems, Inc., Cat. No. AF313) was diluted with 10mL of ice-cold PBS to prepare a 10ug/mL antibody concentration stock. A 96-well microplate (Perkin-Elmer Wallac, cat. no. AAAND-0001) was coated with 100uL of the anti-Tie2 antibody stock and the coated plate was stored at 4°C overnight.

Day 2 - Compound Plate Preparation

The media in the microplate was replaced with a preparation of 500uL DMEM + 1% BSA (Bovine Serum Albumin; ICN Biomedicals, Inc., cat. no. 160069). 20 uL of a selected Tie2 reference compound was placed in a selected well of the 96-well plate, and diluted 1:4 with 100% DMSO from an initial concentration of about 10 mM to a final concentration of about 2.5mM, then diluted 1:3 with 100% DMSO for a 10 point dilution to a final concentration of about 0.128 uM.

Test compounds (10 uL of a 10 mM concentration) were similarly diluted 1:4 with 100% DMSO to obtain a sample concentration of about 2.5mM, then diluted 1:3 for a 10 point dilution to finally obtain a concentration of about 0.128 uM for each test compound. 20 uL of 100% DMSO served as positive controls, while and 10 uL of the 2.5mM concentration of the reference compound served as the negative control.

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A 2 uL aliquot from each well (test compounds, positive and negative controls) in the 96-well plate was added to designated wells in the 24-well cell culture plate (1:250). The culture plate was incubated for 2.5 at 37 °C in
5 an atmosphere of about 5% CO₂.

The Tie-2 ligand was stimulated with the following series of preparations: (1) about 0.5 mL of a protease inhibitor cocktail (Sigma-Aldrich Co., cat. no. P8340) was thawed; (2) to prepare the phosphatase inhibitor, a 300 mM
10 NaVO₄ (Sigma-Aldrich Chem. Co., cat. no. S6508-10G) stock solution in PBS was made and stored at RT. Two 1 mL aliquots of the NaVO₄ solution was prepared in separate two vials by adding 100 uL of the NaVO₄ stock solution to 900 uL RT PBS and each solution was activated by adding 6 uL of
15 H₂O₂ to each vial. Both NaVO₄ solutions were mixed, wrapped in aluminum foil and stored at RT for 15 min.

The Delfia plates, containing 200 uL of PBS + 0.1%TWEEN20, were washed three times and blocked by adding 200 uL of a diluted solution of 5% BSA (16 mL of stock 7.5%
20 BSA solution, available from Perkin-Elmer Wallac, Cat. No. CR84-100, was diluted with 8 mL of room temperature PBS). The plates were then stored at room temperature for about one hour.

100 uL of 35% BSA solution was diluted with 3.4 mL of
25 ice cold PBS to make a 1% BSA/PBS solution. 100 uL of this 1% BSA/ PBS solution was diluted with 900 uL of ice cold PBS. hAng1 was reconstituted with 250 uL of ice cold PBS + 0.1% BSA to make a 100 ug/mL concentration in solution. The solution was separated into 70 uL aliquots and stored at
30 -80 °C.

1mL of the 30 mM solution of NaVO₄/PBS was diluted with 99 mL of ice cold PBS to form a 300 uM concentration. The solution was kept cold on ice. 210 uL of the activated NaVO₄

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and 280 uL of the protease inhibitor preparation was added to 21 mL of RIPA buffer and kept cold on ice.

Dilute hAng1 and stimulate cells:

70uL of the 100ug/mL stock solution was added to 700uL
5 in 1% BSA/DMEM (1:10) to 10ug/mL concentration, and it was stored on ice. 5uL of this 10ug/mL hAng1 preparation was added to each well of the 24-well plate. The plate was shaken at 700 rpm at 37 °C for about 2.5 minutes.

After shaking, the wells were incubated for 7.5 min at
10 37 °C. The media was removed and 400uL of ice cold PBS + 300 uM NaVO₄ was added. The wells were kept on ice for at least 5 min and washed 1 X with ice cold PBS + 300 uM NaVO₄. The wells were tapped against a dry paper towel.

The cells were lysed with 150 uL of RIPA, 300 uM of NaVO₄,
15 and 100 uL/1*10⁷ cells protease inhibitor cocktail (purchased from Sigma-Aldrich, Cat. No. P8340). The solution was incubated, then shaken on ice for 30 min.

The BSA blocking solution was removed from the 96-well plates, which were then tapped dry. 140 uL of cell lysate
20 was added to the antibody-coated plate and the plate was incubated at 4 °C for 2 hours.

Delfia 25X Wash Buffer Concentrate (purchased from Perkin-Elmer Wallac, Cat. No. 1244-114) was diluted with 24 parts DDI water to obtain a washing solution. The lysate
25 was removed and the plate was washed three times each with 400 uL of Delfia washing solution. The plate was tap dried with a paper towel.

The Anti-Phosphotyrosine clone 4G10 (purchased from Upstatebiotech Co., Cat. No. 05-321) was diluted with Delfia
30 Assay Buffer (purchased from Perkin-Elmer Wallac, cat. no. 1244-1111) to make a solution of about 1 ug/mL in concentration. 100 uL of antibody was added to the plate and the plate was incubated at room temperature for one hour.

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The plate was again washed three times with 400 μ L pre-time of the Delfia Washing solution.

The Eu-N1 labeled anti-mouse antibody (purchased from Perkin-Elmer Wallac, cat. no. AD0124) was diluted with
5 Delfia Assay Buffer to make a solution of about 0.1 μ g/mL in concentration.

100 μ L of antibody was added to the plate and the plate was incubated at room temperature for one hour. The plate was again washed with Delfia Wash Buffer three
10 times as described above. 100 μ L of Delfia Enhancement Solution (purchased from Perkin-Elmer Wallac, Cat. No. 1244-105) was added to each well and the plate was incubated at room temperature for 5 min in the dark.

The Europium signal was measured with a Victor
15 multilabel counter (Wallac Model 1420) while shaking (shake fast, linear, .10mm for 1s) using a Europium protocol.

Raw data was analyzed using a fit equation in XLFit. IC₅₀ values were then determined using Grafit software. A majority of the compounds of Examples 1-92 were found to
20 have an IC₅₀ of less than 25 μ M in the Tie-2 cell-based Delfia assay.

The compounds of the invention also were found to have inhibitory activity with respect to other kinase enzymes as well. For example, the compounds were found to be inhibitors
25 of Lck. The exemplary assays described as follows were used to make such determination.

LCK-HOMOGENOUS TIME RESOLVED FLOURESCENT (HTRF) KINASE ASSAY

The LCK HTRF assay begins with LCK in the presence of
30 ATP phosphorylating the biotinylated peptide Gastrin. The reaction incubates for 90 min. To quench the assay detection reagents are added which both stop the reaction by diluting out the enzyme and chelating the metals due to the presence of EDTA. Once the detection reagents are added the

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assay incubates for 30 min to allow for equilibration of the detection reagents.

The LCK HTRF assay is comprised of 10 μ L of compound in 100% DMSO, 15 μ L of ATP and biotinylated Gastrin, and 5 15 μ L of LCK KD GST (225-509) for a final volume of 40 μ L. The final concentration of gastrin is 1.2 μ M. The final concentration of ATP is 0.5 μ M (K_m app= 0.6 μ M \pm 0.1) and the final concentration of LCK is 250pM. Buffer conditions are as follows: 50mM HEPES pH 7.5, 50mM NaCl, 20mM MgCl, 5mM 10 MnCl, 2mM DTT, 0.05% BSA.

The assay is quenched and stopped with 160 μ L of detection reagent. Detection reagents are as follows: Buffer made of 50mM Tris, pH 7.5, 100mM NaCl, 3mM EDTA, 0.05% BSA, 0.1% Tween20. Added to this buffer prior to 15 reading is Steptavidin allophycocyanin (SA-APC) at a final conc in the assay of 0.0004 mg/mL, and europilated anti-phosphotyrosine Ab (Eu-anti-PY) at a final conc of 0.025nM.

The assay plate is read in either a Discovery or a RubyStar. The eu-anti-PY is excited at 320 nm and emits at 20 615 nm to excite the SA-APC which in turn emits at 655 nm. The ratio of SA-APC at 655 nm (excited due to close proximity to the Eu-anti-PY because of phosphorylation of the peptide) to free Eu-anti-PY at 615 nm will give substrate phosphorylation.

25 Assays for other kinases are done in a similar way as described above, varying the concentrations of enzyme, peptide substrate, and ATP added to the reaction, depending on the specific activity of the kinase and measured K_m 's for the substrates.

30 **Human mixed lymphocyte reaction (huMLR):**

The purpose of this assay is to test the potency of T cell activation inhibitors in an *in vitro* model of allogeneic T cell stimulation. Human peripheral blood lymphocytes (hPBL; 2×10^5 /well) are incubated with mitomycin

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C-treated B lymphoblastoid cells (JY cell line; 1×10^5 /well) as allogeneic stimulators in the presence or absence of dilutions of potential inhibitor compound in 96-well round-bottom tissue culture plates. These cultures are incubated at 37 °C in 5% CO₂ for 6 days total. The proliferative response of the hPBL is measured by ³H-thymidine incorporation overnight between days 5 and 6 after initiation of culture. Cells are harvested onto glass fiber filters and ³H-thymidine incorporation into DNA is analyzed by liquid scintillation counter.

Jurkat proliferation/survival assay:

The purpose of this assay is to test the general anti-proliferative/cytotoxic effect of compounds on the Jurkat human T cell line. Jurkat cells (1×10^5 /well) are plated in 96-well flat-bottom tissue culture plates with or without compound dilutions and cultured for 72 h at 37 °C in 5% CO₂. Viable cell number is determined during the last 4 h of culture by adding 10 µL/well WST-1 dye. WST-1 dye conversion relies on active mitochondrial electron transport for reduction of the tetrazolium dye. The dye conversion was read by OD at 450-600 nm.

Anti-CD3/CD28-induced T cell IL-2 secretion and proliferation assay:

The purpose of this assay is to test the potency of T cell receptor (TCR; CD3) and CD28 signaling pathway inhibitors in human T cells. T cells are purified from human peripheral blood lymphocytes (hPBL) and pre-incubated with or without compound prior to stimulation with a combination of an anti-CD3 and an anti-CD28 antibody in 96-well tissue culture plates (1×10^5 T cells/well). Cells are cultured for ~20 h at 37 °C in 5% CO₂, then secreted IL-2 in the supernatants is quantified by cytokine ELISA (Pierce/Endogen). The cells remaining in the wells are then pulsed with ³H-thymidine overnight to assess the T cell

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proliferative response. Cells are harvested onto glass fiber filters and ^3H -thymidine incorporation into DNA is analyzed by liquid scintillation counter. For comparison purposes, phorbol myristic acid (PMA) and calcium ionophore
5 can be used in combination to induce IL-2 secretion from purified T cells. Potential inhibitor compounds can be tested for inhibition of this response as described above for anti-CD3 and -CD28 antibodies.

Assays for other kinases are done in a similar way as
10 described above, varying the concentrations of enzyme, peptide substrate, and ATP added to the reaction, depending on the specific activity of the kinase and measured K_m 's for the substrates.

Exemplary compounds 1-23, 25-54, 56-64, 66-67, 69-77,
15 81-83 and 85-92 exhibited an average IC_{50} value of 10uM or less in the human HTRF assay for the inhibition of the Lck kinase enzyme.

INDICATIONS

Accordingly, compounds of the invention are useful
20 for, but not limited to, the prevention or treatment of inflammation, cancer and related diseases. The compounds of the invention have kinase modulatory activity in general, and kinase inhibitory activity in particular. In one embodiment of the invention, there is provided a method of
25 modulating a protein kinase enzyme in a subject, the method comprising administering to the subject an effective dosage amount of a compound of a compound of Formulae I and II. In another embodiment, the kinase enzyme is abl, Akt, bcr-abl, Blk, Brk, Btk, c-kit, c-Met, c-src, c-fms, CDK1, CDK2, CDK3,
30 CDK4, CDK5, CDK6, CDK7, CDK8, CDK9, CDK10, cRaf1, CSF1R, CSK, EGFR, ErbB2, ErbB3, ErbB4, Erk, Fak, fes, FGFR1, FGFR2, FGFR3, FGFR4, FGFR5, Fgr, flt-1, Fps, Frk, Fyn, Hck, IGF-1R, INS-R, Jak, KDR, Lck, Lyn, MEK, p38, PDGFR, PIK, PKC, PYK2, ros, tie, tie2, TRK, Yes or Zap70.

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Various of the compounds of the invention have selective inhibitory activity for specific kinase receptor enzymes, including Tie-2, Lck, p38 and VEGFR/KDR.

Accordingly, the compounds of the invention would be useful
5 in therapy as antineoplasia agents, anti-inflammatory agents or to minimize deleterious effects of Tie-2, Lck, VEGF and/or p38.

Compounds of the invention would be useful for the treatment of neoplasia including cancer and metastasis,
10 including, but not limited to: carcinoma such as cancer of the bladder, breast, colon, kidney, liver, lung (including small cell lung cancer), esophagus, gall-bladder, ovary, pancreas, stomach, cervix, thyroid, prostate, and skin (including squamous cell carcinoma); hematopoietic tumors of
15 lymphoid lineage (including leukemia, acute lymphocytic leukemia, acute lymphoblastic leukemia, B-cell lymphoma, T-cell-lymphoma, Hodgkin's lymphoma, non-Hodgkin's lymphoma, hairy cell lymphoma and Burkett's lymphoma); hematopoietic tumors of myeloid lineage (including acute and chronic
20 myelogenous leukemias, myelodysplastic syndrome and promyelocytic leukemia); tumors of mesenchymal origin (including fibrosarcoma and rhabdomyosarcoma, and other sarcomas, e.g. soft tissue and bone); tumors of the central and peripheral nervous system (including astrocytoma,
25 neuroblastoma, glioma and schwannomas); and other tumors (including melanoma, seminoma, teratocarcinoma, osteosarcoma, xenoderma pigmentosum, keratocanthoma, thyroid follicular cancer and Kaposi's sarcoma). The compounds are useful for the treatment of neoplasia selected
30 from lung cancer, colon cancer and breast cancer.

The compounds would also be useful for treatment of ophthalmological conditions such as corneal graft rejection, ocular neovascularization, retinal neovascularization including neovascularization following injury or infection,

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diabetic retinopathy, retrolental fibroplasia and neovascular glaucoma; retinal ischemia; vitreous hemorrhage; ulcerative diseases such as gastric ulcer; pathological, but non-malignant, conditions such as hemangiomas, including
5 infantile hemanginomas, angiofibroma of the nasopharynx and avascular necrosis of bone; and disorders of the female reproductive system such as endometriosis. The compounds are also useful for the treatment of edema, and conditions of vascular hyperpermeability.

10 Based on the ability to modulate kinases impacting angiogenesis, the compounds of the invention are also useful in treatment and therapy of proliferative diseases. Particularly, these compounds can be used for the treatment of an inflammatory rheumatoid or rheumatic disease,
15 especially of manifestations at the locomotor apparatus, such as various inflammatory rheumatoid diseases, especially chronic polyarthritis including rheumatoid arthritis, juvenile arthritis or psoriasis arthropathy; paraneoplastic syndrome or tumor-induced inflammatory diseases, turbid
20 effusions, collagenosis, such as systemic Lupus erythematosus, poly-myositis, dermatomyositis, systemic scleroderma or mixed collagenosis; postinfectious arthritis (where no living pathogenic organism can be found at or in the affected part of the body), seronegative
25 spondylarthritis, such as spondylitis ankylosans; vasculitis, sarcoidosis, or arthrosis; or further any combinations thereof. An example of an inflammation related disorder is (a) synovial inflammation, for example, synovitis, including any of the particular forms of
30 synovitis, in particular bursal synovitis and purulent synovitis, as far as it is not crystal-induced. Such synovial inflammation may for example, be consequential to or associated with disease, e.g. arthritis, e.g. osteoarthritis, rheumatoid arthritis or arthritis deformans.

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The present invention is further applicable to the systemic treatment of inflammation, e.g. inflammatory diseases or conditions, of the joints or locomotor apparatus in the region of the tendon insertions and tendon sheaths. Such inflammation may be, for example, consequential to or associated with disease or further (in a broader sense of the invention) with surgical intervention, including, in particular conditions such as insertion endopathy, myofasciale syndrome and tendomyosis. The present invention is further applicable to the treatment of inflammation, e.g. inflammatory disease or condition, of connective tissues including dermatomyositis and myositis.

The compounds of the invention can also be used as active agents against such disease states as arthritis, atherosclerosis, psoriasis, hemangiomas, myocardial angiogenesis, coronary and cerebral collaterals, ischemic limb angiogenesis, wound healing, peptic ulcer Helicobacter related diseases, fractures, cat scratch fever, rubeosis, neovascular glaucoma and retinopathies such as those associated with diabetic retinopathy or macular degeneration. In addition, some of these compounds can be used as active agents against solid tumors, malignant ascites, hematopoietic cancers and hyperproliferative disorders such as thyroid hyperplasia (especially Grave's disease), and cysts (such as hypervascularity of ovarian stroma, characteristic of polycystic ovarian syndrome (Stein- Leventhal syndrome)) since such diseases require a proliferation of blood vessel cells for growth and/or metastasis.

The compounds of the invention can also be used as active agents against burns, chronic lung disease, stroke, polyps, anaphylaxis, chronic and allergic inflammation, ovarian hyperstimulation syndrome, brain tumor-associated cerebral edema, high-altitude, trauma or hypoxia induced

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cerebral or pulmonary edema, ocular and macular edema, ascites, and other diseases where vascular hyperpermeability, effusions, exudates, protein extravasation, or edema is a manifestation of the disease.

5 The compounds will also be useful in treating disorders in which protein extravasation leads to the deposition of fibrin and extracellular matrix, promoting stromal proliferation (e.g. fibrosis, cirrhosis and carpal tunnel syndrome).

10 The compounds of the invention are also useful in the treatment of ulcers including bacterial, fungal, Mooren ulcers and ulcerative colitis.

The compounds of the invention are also useful in the treatment of conditions wherein undesired angiogenesis, edema, or stromal deposition occurs in viral infections such as Herpes simplex, Herpes Zoster, AIDS, Kaposi's sarcoma, protozoan infections and toxoplasmosis, following trauma, radiation, stroke, endometriosis, ovarian hyperstimulation syndrome, systemic lupus, sarcoidosis, synovitis, Crohn's disease, sickle cell anemia, Lyme disease, pemphigoid, Paget's disease, hyperviscosity syndrome, Osler-Weber-Rendu disease, chronic inflammation, chronic occlusive pulmonary disease, asthma, and inflammatory rheumatoid or rheumatic disease. The compounds are also useful in the reduction of sub-cutaneous fat and for the treatment of obesity.

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The compounds of the invention are also useful in the treatment of ocular conditions such as ocular and macular edema, ocular neovascular disease, scleritis, radial keratotomy, uveitis, vitritis, myopia, optic pits, chronic retinal detachment, post-laser complications, glaucoma, conjunctivitis, Stargardt's disease and Eales disease in addition to retinopathy and macular degeneration.

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The compounds of the invention are also useful in the treatment of cardiovascular conditions such as

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atherosclerosis, restenosis, arteriosclerosis, vascular occlusion and carotid obstructive disease.

The compounds of the invention are also useful in the treatment of cancer related indications such as solid
5 tumors, sarcomas (especially Ewing's sarcoma and osteosarcoma), retinoblastoma, rhabdomyosarcomas, neuroblastoma, hematopoietic malignancies, including leukemia and lymphoma, tumor- induced pleural or pericardial effusions, and malignant ascites.

10 The compounds of the invention are also useful in the treatment of diabetic conditions such as diabetic retinopathy and microangiopathy.

The compounds of the present invention are also capable of inhibiting other protein kinases, including for
15 example, Src, fgf, c-Met, ron, ckit and ret, and thus may be effective in the treatment of diseases associated with other protein kinases. More specifically, the compounds of the present invention inhibit the Src-family of protein tyrosine kinases such as Lck, Fyn(B), Fyn(T), Lyn, Src, Yes, Hck, Fgr
20 and Blk, and are thus useful in the treatment, including prevention and therapy, of protein tyrosine kinase-associated disorders such as immunologic disorders. "Protein tyrosine kinase-associated disorders" are those disorders which result from aberrant tyrosine kinase activity, and/or
25 which are alleviated by the inhibition of one or more of these enzymes. For example, Lck inhibitors are of value in the treatment of a number of such disorders (for example, the treatment of autoimmune diseases), as Lck inhibition blocks T cell activation. The treatment of T cell mediated
30 diseases, including inhibition of T cell activation and proliferation, is a preferred embodiment of the present invention. Compounds of the present invention which selectively block T cell activation and proliferation are preferred. Also, compounds of the present invention which

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may block the activation of endothelial cell protein tyrosine kinase by oxidative stress, thereby limiting surface expression of adhesion molecules that induce neutrophil binding, and which can inhibit protein tyrosine kinase necessary for neutrophil activation would be useful, for example, in the treatment of ischemia and reperfusion injury.

The present invention also provides methods for the treatment of protein tyrosine kinase-associated disorders, comprising the step of administering to a subject in need thereof at least one compound of the Formula I or of Formula II in an amount effective therefor. Other therapeutic agents such as those described below may be employed with the inventive compounds in the present methods. In the methods of the present invention, such other therapeutic agent(s) may be administered prior to, simultaneously with or following the administration of the compound(s) of the present invention.

Use of the compound(s) of the present invention in treating protein tyrosine kinase-associated disorders is exemplified by, but is not limited to, treating a range of disorders such as: arthritis (such as rheumatoid arthritis, psoriatic arthritis or osteoarthritis); transplant (such as organ transplant, acute transplant or heterograft or homograft (such as is employed in burn treatment)) rejection; protection from ischemic or reperfusion injury such as ischemic or reperfusion injury incurred during organ transplantation, myocardial infarction, stroke or other causes; transplantation tolerance induction; multiple sclerosis; inflammatory bowel disease, including ulcerative colitis and Crohn's disease; lupus (systemic lupus erythematosus); graft vs. host diseases; T-cell mediated hypersensitivity diseases, including contact hypersensitivity, delayed-type hypersensitivity, and gluten-

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sensitive enteropathy (Celiac disease); Type 1 diabetes; psoriasis; contact dermatitis (including that due to poison ivy); Hashimoto's thyroiditis; Sjogren's syndrome; Autoimmune Hyperthyroidism, such as Graves' Disease;

5 Addison's disease (autoimmune disease of the adrenal glands); Autoimmune polyglandular disease (also known as autoimmune polyglandular syndrome); autoimmune alopecia; pernicious anemia; vitiligo; autoimmune hypopituitarism; Guillain-Barre syndrome; other autoimmune diseases; cancers

10 where Lck or other Src-family kinases such as Src are activated or overexpressed, such as colon carcinoma and thymoma, or cancers where Src-family kinase activity facilitates tumor growth or survival; glomerulonephritis, serum sickness; urticaria; allergic diseases such as

15 respiratory allergies (asthma, hayfever, allergic rhinitis) or skin allergies; scleroderma; mycosis fungoides; acute inflammatory responses (such as acute respiratory distress syndrome and ischemia/reperfusion injury); dermatomyositis; alopecia areata; chronic actinic dermatitis; eczema;

20 Behcet's disease; Pustulosis palmoplantis; Pyoderma gangrenosum; Sezary's syndrome; atopic dermatitis; systemic sclerosis; and morphea. The present invention also provides for a method for treating the aforementioned disorders such as atopic dermatitis by administration of a therapeutically

25 effective amount of a compound of the present invention, which is an inhibitor of protein tyrosine kinase, to a patient in need of such treatment.

Src-family kinases other than Lck, such as Hck and Fgr, are important in the Fcγ receptor induced respiratory

30 burst of neutrophils as well as the Fcγ receptor responses of monocytes and macrophages. The compounds of the present invention may inhibit the Fcγ induced respiratory burst response in neutrophils, and may also inhibit the Fcγ dependent production of TNFα. The ability to inhibit Fcγ

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receptor dependent neutrophil, monocyte and macrophage responses would result in additional anti-inflammatory activity for the present compounds in addition to their effects on T cells. This activity would be especially of value, for example, in the treatment of inflammatory diseases, such as arthritis or inflammatory bowel disease.

The present compounds may also be of value for the treatment of autoimmune glomerulonephritis and other instances of glomerulonephritis induced by deposition of immune complexes in the kidney that trigger Fc γ receptor responses and which can lead to kidney damage.

In addition, certain Src family kinases, such as Lyn and Fyn(B), may be important in the Fc ϵ receptor induced degranulation of mast cells and basophils that plays an important role in asthma, allergic rhinitis, and other allergic disease. Fc ϵ receptors are stimulated by IgE-antigen complexes. The compounds of the present invention may inhibit the Fc ϵ induced degranulation responses. The ability to inhibit Fc ϵ receptor dependent mast cell and basophil responses may result in additional anti-inflammatory activity for the present compounds beyond their effect on T cells.

The combined activity of the present compounds towards monocytes, macrophages, T cells, etc. may prove to be a valuable tool in the treatment of any of the aforementioned disorders.

In a particular embodiment, the compounds of the present invention are useful for the treatment of the aforementioned exemplary disorders irrespective of their etiology, for example, for the treatment of rheumatoid arthritis, transplant rejection, multiple sclerosis, inflammatory bowel disease, lupus, graft v. host disease, T cell mediated hypersensitivity disease, psoriasis, Hashimoto's thyroiditis, Guillain-Barre syndrome, cancer,

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contact dermatitis, allergic disease such as allergic rhinitis, asthma, ischemic or reperfusion injury, or atopic dermatitis whether or not associated with PTK.

In another embodiment, the compounds are useful for the treatment of rheumatoid spondylitis, gouty arthritis, adult respiratory distress syndrome (ARDS), anaphylaxis, muscle degeneration, cachexia, Reiter's syndrome, type II diabetes, bone resorption diseases, graft vs. host reaction, Alzheimer's disease, atherosclerosis, brain trauma, multiple sclerosis, cerebral malaria, sepsis, septic shock, toxic shock syndrome, fever, and myalgias due to infection, or which subject is infected by HIV-1, HIV-2, HIV-3, cytomegalovirus (CMV), influenza, adenovirus, the herpes viruses (including HSV-1, HSV-2), or herpes zoster in a subject, the method comprising administering to the subject a pharmaceutical composition comprising an effective dosage amount of a compound according to any of Claims 1-16.

Besides being useful for human treatment, these compounds are useful for veterinary treatment of companion animals, exotic animals and farm animals, including mammals, rodents, and the like. For example, animals including horses, dogs, and cats may be treated with compounds provided by the invention.

FORMULATIONS AND METHOD OF USE

Treatment of diseases and disorders herein is intended to also include therapeutic administration of a compound of the invention, or a pharmaceutical salt thereof, or a pharmaceutical composition of either to a subject (i.e., an animal, preferably a mammal, most preferably a human) which may be in need of preventative treatment, such as, for example, for pain, inflammation, cancer and the like. Treatment also encompasses prophylactic administration of a compound of the invention, or a pharmaceutical salt thereof, or a pharmaceutical composition of either to a subject

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(i.e., an animal, preferably a mammal, most preferably a human). Generally, the subject is initially diagnosed by a licensed physician and/or authorized medical practitioner, and a regimen for prophylactic and/or therapeutic treatment
5 via administration of the compound(s) or compositions of the invention is suggested, recommended or prescribed.

While it may be possible to administer a compound of the invention alone, in the methods described, the compound administered normally will be present as an active
10 ingredient in a pharmaceutical composition. Thus, in another embodiment of the invention, there is provided a pharmaceutical composition comprising a compound of this invention in combination with a pharmaceutically acceptable carrier, which includes diluents, excipients, adjuvants and
15 the like (collectively referred to herein as "carrier" materials) as described herein, and, if desired, other active ingredients. A pharmaceutical composition of the invention may comprise an effective amount of a compound of the invention or an effective dosage amount of a compound of
20 the invention. An effective dosage amount of a compound of the invention includes an amount less than, equal to or greater than an effective amount of the compound; for example, a pharmaceutical composition in which two or more unit dosages, such as in tablets, capsules and the like, are
25 required to administer an effective amount of the compound, or alternatively, a multi-dose pharmaceutical composition, such as powders, liquids and the like, in which an effective amount of the compound is administered by administering a portion of the composition.

30 The compound(s) of the present invention may be administered by any suitable route, preferably in the form of a pharmaceutical composition adapted to such a route, and in a dose effective for the treatment intended. The compounds and compositions of the present invention may, for

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example, be administered orally, mucosally, topically, rectally, pulmonarily such as by inhalation spray, or parentally including intravascularly, intravenously, intraperitoneally, subcutaneously, intramuscularly
5 intrasternally and infusion techniques, in dosage unit formulations containing conventional pharmaceutically acceptable carriers, adjuvants, and vehicles.

For oral administration, the pharmaceutical composition may be in the form of, for example, a tablet,
10 capsule, suspension or liquid. The pharmaceutical composition is preferably made in the form of a dosage unit containing a particular amount of the active ingredient. Examples of such dosage units are tablets or capsules. For example, these may contain an amount of active ingredient
15 from about 1 to 2000 mg, and typically from about 1 to 500 mg. A suitable daily dose for a human or other mammal may vary widely depending on the condition of the patient and other factors, but, once again, can be determined using routine methods and practices.

20 The amount of compounds which are administered and the dosage regimen for treating a disease condition with the compounds and/or compositions of this invention depends on a variety of factors, including the age, weight, sex and medical condition of the subject, the type of disease, the
25 severity of the disease, the route and frequency of administration, and the particular compound employed. Thus, the dosage regimen may vary widely, but can be determined routinely using standard methods. A daily dose of about 0.01 to 500 mg/kg, advantageously between about 0.01 and
30 about 50 mg/kg, and more advantageously about 0.01 and about 30 mg/kg body weight may be appropriate. The daily dose can be administered in one to four doses per day.

For therapeutic purposes, the active compounds of this invention are ordinarily combined with one or more adjuvants

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or "excipients" appropriate to the indicated route of administration. If administered on a per dose basis, the compounds may be admixed with lactose, sucrose, starch powder, cellulose esters of alkanolic acids, cellulose alkyl esters, talc, stearic acid, magnesium stearate, magnesium oxide, sodium and calcium salts of phosphoric and sulfuric acids, gelatin, acacia gum, sodium alginate, polyvinylpyrrolidone, and/or polyvinyl alcohol, to form the final formulation. For example, the active compound(s) and excipient(s) may be tableted or encapsulated by known and accepted methods for convenient administration. Examples of suitable formulations include, without limitation, pills, tablets, soft and hard-shell gel capsules, troches, orally-dissolvable forms and delayed or controlled-release formulations thereof. Particularly, capsule or tablet formulations may contain one or more controlled-release agents, such as hydroxypropylmethyl cellulose, as a dispersion with the active compound(s).

In the case of psoriasis and other skin conditions, it may be preferable to apply a topical preparation of compounds of this invention to the affected area two to four times a day.

Formulations suitable for topical administration include liquid or semi-liquid preparations suitable for penetration through the skin (e.g., liniments, lotions, ointments, creams, pastes, suspensions and the like) and drops suitable for administration to the eye, ear, or nose. A suitable topical dose of active ingredient of a compound of the invention is 0.1 mg to 150 mg administered one to four, preferably one or two times daily. For topical administration, the active ingredient may comprise from 0.001% to 10% w/w, e.g., from 1% to 2% by weight of the formulation, although it may comprise as much as 10% w/w,

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but preferably not more than 5% w/w, and more preferably from 0.1% to 1% of the formulation.

When formulated in an ointment, the active ingredients may be employed with either paraffinic or a water-miscible ointment base. Alternatively, the active ingredients may be formulated in a cream with an oil-in-water cream base. If desired, the aqueous phase of the cream base may include, for example at least 30% w/w of a polyhydric alcohol such as propylene glycol, butane-1,3-diol, mannitol, sorbitol, glycerol, polyethylene glycol and mixtures thereof. The topical formulation may desirably include a compound, which enhances absorption or penetration of the active ingredient through the skin or other affected areas. Examples of such dermal penetration enhancers include DMSO and related analogs.

The compounds of this invention can also be administered by transdermal device. Preferably transdermal administration will be accomplished using a patch either of the reservoir and porous membrane type or of a solid matrix variety. In either case, the active agent is delivered continuously from the reservoir or microcapsules through a membrane into the active agent permeable adhesive, which is in contact with the skin or mucosa of the recipient. If the active agent is absorbed through the skin, a controlled and predetermined flow of the active agent is administered to the recipient. In the case of microcapsules, the encapsulating agent may also function as the membrane.

The oily phase of the emulsions of this invention may be constituted from known ingredients in a known manner. While the phase may comprise merely an emulsifier, it may comprise a mixture of at least one emulsifier with a fat or an oil or with both a fat and an oil. Preferably, a hydrophilic emulsifier is included together with a lipophilic emulsifier which acts as a stabilizer. It is

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also preferred to include both an oil and a fat. Together, the emulsifier(s) with or without stabilizer(s) make-up the so-called emulsifying wax, and the wax together with the oil and fat make up the so-called emulsifying ointment base, which forms the oily dispersed phase of the cream formulations. Emulsifiers and emulsion stabilizers suitable for use in the formulation of the present invention include, for example, Tween 60, Span 80, cetostearyl alcohol, myristyl alcohol, glyceryl monostearate, sodium lauryl sulfate, glyceryl distearate alone or with a wax, or other materials well known in the art.

The choice of suitable oils or fats for the formulation is based on achieving the desired cosmetic properties, since the solubility of the active compound in most oils likely to be used in pharmaceutical emulsion formulations is very low. Thus, the cream should preferably be a non-greasy, non-staining and washable product with suitable consistency to avoid leakage from tubes or other containers. Straight or branched chain, mono- or dibasic alkyl esters such as di-isoadipate, isocetyl stearate, propylene glycol diester of coconut fatty acids, isopropyl myristate, decyl oleate, isopropyl palmitate, butyl stearate, 2-ethylhexyl palmitate or a blend of branched chain esters may be used. These may be used alone or in combination depending on the properties required. Alternatively, high melting point lipids such as white soft paraffin and/or liquid paraffin or other mineral oils can be used.

Formulations suitable for topical administration to the eye also include eye drops wherein the active ingredients are dissolved or suspended in suitable carrier, especially an aqueous solvent for the active ingredients. The active ingredients are preferably present in such

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formulations in a concentration of 0.5 to 20%,
advantageously 0.5 to 10% and particularly about 1.5% w/w.

Formulations for parenteral administration may be in
the form of aqueous or non-aqueous isotonic sterile
5 injection solutions or suspensions. These solutions and
suspensions may be prepared from sterile powders or granules
using one or more of the carriers or diluents mentioned for
use in the formulations for oral administration or by using
other suitable dispersing or wetting agents and suspending
10 agents. The compounds may be dissolved in water,
polyethylene glycol, propylene glycol, ethanol, corn oil,
cottonseed oil, peanut oil, sesame oil, benzyl alcohol,
sodium chloride, tragacanth gum, and/or various buffers.
Other adjuvants and modes of administration are well and
15 widely known in the pharmaceutical art. The active
ingredient may also be administered by injection as a
composition with suitable carriers including saline,
dextrose, or water, or with cyclodextrin (ie. Captisol),
cosolvent solubilization (ie. propylene glycol) or micellar
20 solubilization (ie. Tween 80).

The sterile injectable preparation may also be a
sterile injectable solution or suspension in a non-toxic
parenterally acceptable diluent or solvent, for example as a
solution in 1,3-butanediol. Among the acceptable vehicles
25 and solvents that may be employed are water, Ringer's
solution, and isotonic sodium chloride solution. In
addition, sterile, fixed oils are conventionally employed as
a solvent or suspending medium. For this purpose any bland
fixed oil may be employed, including synthetic mono- or
30 diglycerides. In addition, fatty acids such as oleic acid
find use in the preparation of injectables.

The active ingredient may also be administered by injection
as a composition with suitable carriers including saline,
dextrose, or water. The daily parenteral dosage regimen

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will be from about 0.1 to about 30 mg/kg of total body weight, preferably from about 0.1 to about 10 mg/kg, and more preferably from about 0.25 mg to 1 mg/kg.

For pulmonary administration, the pharmaceutical
5 composition may be administered in the form of an aerosol or with an inhaler including dry powder aerosol.

Suppositories for rectal administration of the drug can be prepared by mixing the drug with a suitable non-irritating excipient such as cocoa butter and polyethylene
10 glycols that are solid at ordinary temperatures but liquid at the rectal temperature and will therefore melt in the rectum and release the drug.

The pharmaceutical compositions may be subjected to conventional pharmaceutical operations such as sterilization
15 and/or may contain conventional adjuvants, such as preservatives, stabilizers, wetting agents, emulsifiers, buffers etc. Tablets and pills can additionally be prepared with enteric coatings. Such compositions may also comprise adjuvants, such as wetting, sweetening, flavoring, and
20 perfuming agents.

COMBINATIONS

While the compounds of the invention can be dosed or administered as the sole active pharmaceutical agent, they can also be used in combination with one or more compounds
25 of the invention or in conjunction with other agents. When administered as a combination, the therapeutic agents can be formulated as separate compositions that are administered simultaneously or sequentially at different times, or the therapeutic agents can be given as a single composition.

30 The phrase "co-therapy" (or "combination-therapy"), in defining use of a compound of the present invention and another pharmaceutical agent, is intended to embrace administration of each agent in a sequential manner in a regimen that will provide beneficial effects of the drug

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combination, and is intended as well to embrace co-administration of these agents in a substantially simultaneous manner, such as in a single capsule having a fixed ratio of these active agents or in multiple, separate capsules for each agent.

Specifically, the administration of compounds of the present invention may be in conjunction with additional therapies known to those skilled in the art in the prevention or treatment of neoplasia, such as with radiation therapy or with cytostatic or cytotoxic agents.

If formulated as a fixed dose, such combination products employ the compounds of this invention within the accepted dosage ranges. Compounds of Formulas I - III may also be administered sequentially with known anticancer or cytotoxic agents when a combination formulation is inappropriate. The invention is not limited in the sequence of administration; compounds of the invention may be administered either prior to, simultaneous with or after administration of the known anticancer or cytotoxic agent.

Currently, standard treatment of primary tumors consists of surgical excision followed by either radiation or IV administered chemotherapy. The typical chemotherapy regime consists of either DNA alkylating agents, DNA intercalating agents, CDK inhibitors, or microtubule poisons. The chemotherapy doses used are just below the maximal tolerated dose and therefore dose limiting toxicities typically include, nausea, vomiting, diarrhea, hair loss, neutropenia and the like.

There are large numbers of antineoplastic agents available in commercial use, in clinical evaluation and in pre-clinical development, which would be selected for treatment of neoplasia by combination drug chemotherapy. Such antineoplastic agents fall into several major categories, namely, antibiotic-type agents, alkylating

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agents, antimetabolite agents, hormonal agents, immunological agents, interferon-type agents and a category of miscellaneous agents.

5 A first family of antineoplastic agents, which may be used in combination with compounds of the invention consists of antimetabolite-type/thymidilate synthase inhibitor antineoplastic agents. Suitable antimetabolite antineoplastic agents may be selected from but not limited to the group consisting of 5-FU-fibrinogen, acanthifolic
10 acid, aminothiadiaazole, brequinar sodium, carmofur, Ciba-Geigy CGP-30694, cyclopentyl cytosine, cytarabine phosphate stearate, cytarabine conjugates, Lilly DATHF, Merrel Dow DDFC, dezaguanine, dideoxycytidine, dideoxyguanosine, didox, Yoshitomi DMDC, doxifluridine, Wellcome EHNA, Merck & Co.
15 EX-015, fazarabine, floxuridine, fludarabine phosphate, 5-fluorouracil, N-(2'-furanidyl)-5-fluorouracil, Daiichi Seiyaku FO-152, isopropyl pyrrolizine, Lilly LY-188011, Lilly LY-264618, methobenzaprim, methotrexate, Wellcome MZPES, norspermidine, NCI NSC-127716, NCI NSC-264880, NCI
20 NSC-39661, NCI NSC-612567, Warner-Lambert PALA, pentostatin, piritrexim, plicamycin, Asahi Chemical PL-AC, Takeda TAC-788, thioguanine, tiazofurin, Erbamont TIF, trimetrexate, tyrosine kinase inhibitors, Taiho UFT and uricytin.

A second family of antineoplastic agents, which may be
25 used in combination with compounds of the invention consists of alkylating-type antineoplastic agents. Suitable alkylating-type antineoplastic agents may be selected from but not limited to the group consisting of Shionogi 254-S, aldo-phosphamide analogues, altretamine, anaxirone,
30 Boehringer Mannheim BBR-2207, bestrabucil, budotitane, Wakunaga CA-102, carboplatin, carmustine, Chinoin-139, Chinoin-153, chlorambucil, cisplatin, cyclophosphamide, American Cyanamid CL-286558, Sanofi CY-233, cyplatate, Degussa D-19-384, Sumimoto DACHP(Myrr)2,

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diphenylspiromustine, diplatinum cytostatic, Erba distamycin derivatives, Chugai DWA-2114R, ITI E09, elmustine, Erbamont FCE-24517, estramustine phosphate sodium, fotemustine, Unimed G-6-M, Chinoin GYKI-17230, hepsul-fam, ifosfamide, 5 iproplatin, lomustine, mafosfamide, mitolactol, Nippon Kayaku NK-121, NCI NSC-264395, NCI NSC-342215, oxaliplatin, Upjohn PCNU, prednimustine, Proter PTT-119, ranimustine, semustine, SmithKline SK&F-101772, Yakult Honsha SN-22, spiromustine, Tanabe Seiyaku TA-077, tauromustine, 10 temozolomide, teroxirone, tetraplatin and trimelamol.

A third family of antineoplastic agents which may be used in combination with compounds of the invention consists of antibiotic-type antineoplastic agents. Suitable antibiotic-type antineoplastic agents may be selected from 15 but not limited to the group consisting of Taiho 4181-A, aclarubicin, actinomycin D, actinoplanone, Erbamont ADR-456, aeroplysinin derivative, Ajinomoto AN-201-II, Ajinomoto AN-3, Nippon Soda anisomycins, anthracycline, azino-mycin-A, bisucaberin, Bristol-Myers BL-6859, Bristol-Myers BMY-25067, 20 Bristol-Myers BMY-25551, Bristol-Myers BMY-26605, Bristol-Myers BMY-27557, Bristol-Myers BMY-28438, bleomycin sulfate, bryostatin-1, Taiho C-1027, caliche mycin, chromoximycin, dactinomycin, daunorubicin, Kyowa Hakko DC-102, Kyowa Hakko DC-79, Kyowa Hakko DC-88A, Kyowa Hakko DC89-A1, Kyowa Hakko 25 DC92-B, ditrisarubicin B, Shionogi DOB-41, doxorubicin, doxorubicin-fibrinogen, elsamicin-A, epirubicin, erbstatin, esorubicin, esperamicin-A1, esperamicin-Alb, Erbamont FCE-21954, Fujisawa FK-973, fostriecin, Fujisawa FR-900482, glidobactin, gregatin-A, grincamycin, herbimycin, 30 idarubicin, illudins, kazusamycin, kesarirhodins, Kyowa Hakko KM-5539, Kirin Brewery KRN-8602, Kyowa Hakko KT-5432, Kyowa Hakko KT-5594, Kyowa Hakko KT-6149, American Cyanamid LL-D49194, Meiji Seika ME 2303, menogaril, mitomycin, mitoxantrone, SmithKline M-TAG, neoenactin, Nippon Kayaku

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NK-313, Nippon Kayaku NKT-01, SRI International NSC-357704, oxalysine, oxaunomycin, peplomycin, pilatin, pirarubicin, porothramycin, pyrindanycin A, Tobishi RA-I, rapamycin, rhizoxin, rodorubicin, sibanomicin, siwenmycin, Sumitomo SM-5887, Snow Brand SN-706, Snow Brand SN-07, sorangicin-A, sparsomycin, SS Pharmaceutical SS-21020, SS Pharmaceutical SS-7313B, SS Pharmaceutical SS-9816B, steffimycin B, Taiho 4181-2, talisomycin, Takeda TAN-868A, terpentecin, thrazine, tricrozarin A, Upjohn U-73975, Kyowa Hakko UCN-10028A, Fujisawa WF-3405, Yoshitomi Y-25024 and zorubicin.

A fourth family of antineoplastic agents which may be used in combination with compounds of the invention consists of a miscellaneous family of antineoplastic agents, including tubulin interacting agents, topoisomerase II inhibitors, topoisomerase I inhibitors and hormonal agents, selected from but not limited to the group consisting of α -carotene, α -difluoromethyl-arginine, acitretin, Biotec AD-5, Kyorin AHC-52, alstonine, amonafide, amphetinile, amsacrine, Angiostat, ankinomycin, anti-neoplaston A10, antineoplaston A2, antineoplaston A3, antineoplaston A5, antineoplaston AS2-1, Henkel APD, aphidicolin glycinate, asparaginase, Avarol, baccharin, batracylin, benfluron, benzotript, Ipsen-Beaufour BIM-23015, bisantrene, Bristol-Myers BMY-40481, Vestar boron-10, bromofosfamide, Wellcome BW-502, Wellcome BW-773, caracemide, carmethizole hydrochloride, Ajinomoto CDAF, chlorsulfaquinoxalone, Chemes CHX-2053, Chemex CHX-100, Warner-Lambert CI-921, Warner-Lambert CI-937, Warner-Lambert CI-941, Warner-Lambert CI-958, clanfenur, claviridenone, ICN compound 1259, ICN compound 4711, Contracan, Yakult Honsha CPT-11, crisnatol, curaderm, cytochalasin B, cytarabine, cytoctin, Merz D-609, DABIS maleate, dacarbazine, datelliptinium, didemnin-B, dihaematoporphyrin ether, dihydrolenperone, dinaline, distamycin, Toyo Pharmar DM-341, Toyo Pharmar DM-75, Daiichi

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Seiyaku DN-9693, docetaxel elliprabin, elliptinium acetate, Tsumura EPMTc, the epothilones, ergotamine, etoposide, etretinate, fenretinide, Fujisawa FR-57704, gallium nitrate, genkwadaphnin, Chugai GLA-43, Glaxo GR-63178, grifolan NMF-5N, hexadecylphosphocholine, Green Cross HO-221, homoharringtonine, hydroxyurea, BTG ICRF-187, ilmofosine, isoglutamine, isotretinoin, Otsuka JI-36, Ramot K-477, Otsuka K-76COONa, Kureha Chemical K-AM, MECT Corp KI-8110, American Cyanamid L-623, leukoregulin, lonidamine, Lundbeck LU-23-112, Lilly LY-186641, NCI (US) MAP, marycin, Merrel Dow MDL-27048, Medco MEDR-340, merbarone, merocyanine derivatives, methylanilinoacridine, Molecular Genetics MGI-136, minactivin, mitonafide, mitoquinone mepidamol, motretinide, Zenyaku Kogyo MST-16, N-(retinoyl)amino acids, Nisshin Flour Milling N-021, N-acylated-dehydroalanines, nafazatrom, Taisho NCU-190, nocodazole derivative, Normosang, NCI NSC-145813, NCI NSC-361456, NCI NSC-604782, NCI NSC-95580, ocreotide, Ono ONO-112, oquizarone, Akzo Org-10172, paclitaxel, pancratistatin, pazelliptine, Warner-Lambert PD-111707, Warner-Lambert PD-115934, Warner-Lambert PD-131141, Pierre Fabre PE-1001, ICRT peptide D, piroxantrone, polyhaematoporphyrin, polypreic acid, Efamol porphyrin, probimane, procarbazine, proglumide, Invitron protease nexin I, Tobishi RA-700, razoxane, Sapporo Breweries RBS, restrictin-P, retelliptine, retinoic acid, Rhone-Poulenc RP-49532, Rhone-Poulenc RP-56976, SmithKline SK&F-104864, Sumitomo SM-108, Kuraray SMANCS, SeaPharm SP-10094, spatol, spirocyclopropane derivatives, spirogermanium, Unimed, SS Pharmaceutical SS-554, strypoldinone, Stypoldione, Suntory SUN 0237, Suntory SUN 2071, superoxide dismutase, Toyama T-506, Toyama T-680, taxol, Teijin TEI-0303, teniposide, thaliblastine, Eastman Kodak TJB-29, tocotrienol, topotecan, Topostin, Teijin TT-82, Kyowa Hakko UCN-01, Kyowa Hakko UCN-1028, ukrain,

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Eastman Kodak USB-006, vinblastine sulfate, vincristine, vindesine, vinestramide, vinorelbine, vintriptol, vinzolidine, withanolides and Yamanouchi YM-534.

Alternatively, the compounds of the invention may also
5 be used in co-therapies with other anti-neoplastic agents, such as acemannan, aclarubicin, aldesleukin, alemtuzumab, alitretinoin, altretamine, amifostine, aminolevulinic acid, amrubicin, amsacrine, anagrelide, anastrozole, ANCER, ancestim, ARGLABIN, arsenic trioxide, BAM 002 (Novelos),
10 bexarotene, bicalutamide, broxuridine, capecitabine, celmoleukin, cetorelix, cladribine, clotrimazole, cytarabine ocfosfate, DA 3030 (Dong-A), daclizumab, denileukin diftitox, deslorelin, dexrazoxane, dilazep, docetaxel, docosanol, doxercalciferol, doxifluridine,
15 doxorubicin, bromocriptine, carmustine, cytarabine, fluorouracil, HIT diclofenac, interferon alfa, daunorubicin, doxorubicin, tretinoin, edelfosine, edrecolomab, eflornithine, emitefur, epirubicin, epoetin beta, etoposide phosphate, exemestane, exisulind, fadrozole, filgrastim,
20 finasteride, fludarabine phosphate, formestane, fotemustine, gallium nitrate, gemcitabine, gemtuzumab zogamicin, gimeracil/oteracil/tegafur combination, glycopine, goserelin, heptaplatin, human chorionic gonadotropin, human fetal alpha fetoprotein, ibandronic acid, idarubicin,
25 (imiquimod, interferon alfa, interferon alfa, natural, interferon alfa-2, interferon alfa-2a, interferon alfa-2b, interferon alfa-N1, interferon alfa-n3, interferon alfacon-1, interferon alpha, natural, interferon beta, interferon beta-1a, interferon beta-1b, interferon gamma, natural
30 interferon gamma-1a, interferon gamma-1b, interleukin-1 beta, iobenguane, irinotecan, irsogladine, lanreotide, LC 9018 (Yakult), leflunomide, lenograstim, lentinan sulfate, letrozole, leukocyte alpha interferon, leuprorelin, levamisole + fluorouracil, liarozole, lobaplatin,

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lonidamine, lovastatin, masoprocol, melarsoprol,
metoclopramide, mifepristone, miltefosine, mirimostim,
mismatched double stranded RNA, mitoguazone, mitolactol,
mitoxantrone, molgramostim, nafarelin, naloxone +
5 pentazocine, nartograstim, nedaplatin, nilutamide,
noscaphine, novel erythropoiesis stimulating protein, NSC
631570 octreotide, oprelvekin, osaterone, oxaliplatin,
paclitaxel, pamidronic acid, pegaspargase, peginterferon
alfa-2b, pentosan polysulfate sodium, pentostatin,
10 picibanil, pirarubicin, rabbit antithymocyte polyclonal
antibody, polyethylene glycol interferon alfa-2a, porfimer
sodium, raloxifene, raltitrexed, rasburicase, rhenium Re 186
etidronate, RII retinamide, rituximab, romurtide, samarium
(153 Sm) lexicidronam, sargramostim, sizofiran, sobuzoxane,
15 sonermin, strontium-89 chloride, suramin, tasonermin,
tazarotene, tegafur, temoporfin, temozolomide, teniposide,
tetrachlorodecaoxide, thalidomide, thymalfasin, thyrotropin
alfa, topotecan, toremifene, tositumomab-iodine 131,
trastuzumab, treosulfan, tretinoin, trilostane,
20 trimetrexate, triptorelin, tumor necrosis factor alpha,
natural, ubenimex, bladder cancer vaccine, Maruyama vaccine,
melanoma lysate vaccine, valrubicin, verteporfin,
vinorelbine, VIRULIZIN, zinostatin stimalamer, or zoledronic
acid; abarelix; AE 941 (Aeterna), ambamustine, antisense
25 oligonucleotide, bcl-2 (Genta), APC 8015 (Dendreon),
cetuximab, decitabine, dexaminoglutethimide, diaziquone, EL
532 (Elan), EM 800 (Endorecherche), eniluracil, etanidazole,
fenretinide, filgrastim SD01 (Amgen), fulvestrant,
galocitabine, gastrin 17 immunogen, HLA-B7 gene therapy
30 (Vical), granulocyte macrophage colony stimulating factor,
histamine dihydrochloride, ibritumomab tiuxetan, ilomastat,
IM 862 (Cytran), interleukin-2, iproxifene, LDI 200
(Milkhaus), leridistim, lintuzumab, CA 125 MAb (Biomira),
cancer MAb (Japan Pharmaceutical Development), HER-2 and Fc

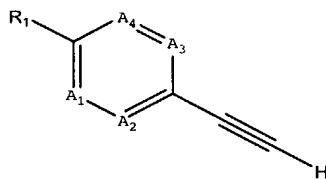
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MAb (Medarex), idiotypic 105AD7 MAb (CRC Technology),
 idiotypic CEA MAb (Trilex), LYM-1-iodine 131 MAb
 (Techniclone), polymorphic epithelial mucin-yttrium 90 MAb
 (Antisoma), marimastat, menogaril, mitumomab, motexafin
 5 gadolinium, MX 6 (Galderma), nelarabine, nolatrexed, P 30
 protein, pegvisomant, pemetrexed, porfiromycin, prinomastat,
 RL 0903 (Shire), rubitecan, satraplatin, sodium
 phenylacetate, sparfosic acid, SRL 172 (SR Pharma), SU 5416
 (SUGEN), TA 077 (Tanabe), tetrathiomolybdate, thaliblastine,
 10 thrombopoietin, tin ethyl etiopurpurin, tirapazamine, cancer
 vaccine (Biomira), melanoma vaccine (New York University),
 melanoma vaccine (Sloan Kettering Institute), melanoma
 oncolysate vaccine (New York Medical College), viral
 melanoma cell lysates vaccine (Royal Newcastle Hospital), or
 15 valspodar.

Alternatively, the compounds of the invention may also
 be used in co-therapies with other anti-neoplastic agents,
 such as other kinase inhibitors including p38 inhibitors and
 CDK inhibitors, TNF inhibitors, metallomatrix proteases
 20 inhibitors (MMP), COX-2 inhibitors including celecoxib,
 rofecoxib, parecoxib, valdecoxib, and etoricoxib, NSAID's,
 SOD mimics or $\alpha_v\beta_3$ inhibitors.

The invention also provides processes for making
 compounds for Formula I, the method comprising the step of A
 25 process of making a compound of Formula I, the process
 comprising the step of

reacting a compound of Formula A,



A

30 wherein A¹, A², A³, A⁴ and R¹ are as defined in Claim 1,
 with a compound of Formula B, X-R² wherein X is a halogen

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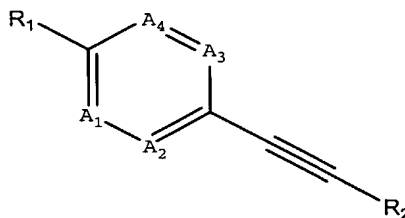
selected from bromine and iodine and R^2 is as defined in claim 1, to form a compound of formula I.

The foregoing description is merely illustrative of the invention and is not intended to limit the invention to
5 the disclosed compounds, compositions and methods. Variations and changes, which are obvious to one skilled in the art, are intended to be within the scope and nature of the invention, as defined in the appended claims. From the foregoing description, one skilled in the art can easily
10 ascertain the essential characteristics of this invention, and without departing from the spirit and scope thereof, can make various changes and modifications of the invention to adapt it to various usages and conditions. All patents and other publications recited herein are hereby incorporated by
15 reference in their entireties.

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What is claimed is:

1. A compound of Formula I:



5

I

or stereoisomer, tautomer, solvate, pharmaceutically acceptable salt, derivative or prodrug thereof, wherein

A¹ is CR³ or N;

A² is CR⁴ or N;

10

A³ is CR⁵ or N;

A⁴ is CR⁶ or N;

provided that at least one of A¹, A², A³ and A⁴ is N and no more than three of A¹, A², A³ and A⁴ are N;

15 R¹ is NR⁷R⁷, NR⁷R⁸, SR⁷, OR⁸, SR⁸, C(O)R⁷, OC(O)R⁷, COOR⁷, C(O)R⁸, OC(O)R⁸, COOR⁸, C(O)NR⁷R⁷, C(S)NR⁷R⁷, NR⁷C(O)R⁷, NR⁷C(S)R⁷, NR⁷C(O)NR⁷R⁷, NR⁷C(S)NR⁷R⁷, NR⁷(COOR⁷), OC(O)NR⁷R⁷, C(O)NR⁷R⁸, C(S)NR⁷R⁸, NR⁷C(O)R⁸, NR⁷C(S)R⁸, NR⁷C(O)NR⁷R⁸, NR⁷C(S)NR⁷R⁸, NR⁷(COOR⁸), OC(O)NR⁷R⁸, S(O)₂NR⁷R⁷, NR⁷S(O)₂NR⁷R⁷, NR⁷S(O)₂R⁷, S(O)₂R⁸, S(O)₂NR⁷R⁸, NR⁷S(O)₂NR⁷R⁸ or NR⁷S(O)₂R⁸;

20

R² is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, wherein said ring system is substituted independently with

25 one or more substituents of R¹⁰, R¹¹, R¹⁵, NR¹⁰R¹⁰, NR¹⁰R¹¹, OR¹⁰, SR¹⁰, OR¹¹, SR¹¹, C(O)R¹⁰, C(S)R¹⁰, C(NCN)R¹⁰, C(O)R¹¹, C(S)R¹¹, C(NCN)R¹¹, C(O)C(O)R¹⁰, OC(O)R¹⁰, COOR¹⁰, C(O)SR¹⁰, C(O)C(O)R¹¹, 30 OC(O)R¹¹, COOR¹¹, C(O)SR¹¹, C(O)NR¹⁰R¹⁰, C(S)NR¹⁰R¹⁰, C(O)NR¹⁰R¹¹,

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- $C(S)NR^{10}R^{11}$, $OC(O)NR^{10}R^{11}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)R^{11}$, $NR^{10}C(S)R^{10}$,
 $NR^{10}C(S)R^{11}$, $NR^{10}C(O)NR^{10}R^{10}$, $NR^{10}C(O)NR^{10}R^{11}$, $NR^{10}C(S)NR^{10}R^{10}$,
 $NR^{10}C(S)NR^{10}R^{11}$, $NR^{10}(COOR^{10})$, $NR^{10}(COOR^{11})$, $NR^{10}C(O)C(O)R^{10}$,
 $NR^{10}C(O)C(O)R^{11}$, $NR^{10}C(O)C(O)NR^{10}R^{11}$, $S(O)_2R^{10}$, $S(O)_2R^{11}$,
5 $S(O)_2NR^{10}R^{10}$, $S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2R^{10}$ or
 $NR^{10}S(O)_2R^{11}$, provided that at least one substituent on said
ring system is $C(O)C(O)R^{10}$, $OC(O)R^{10}$, $COOR^{10}$, $C(O)SR^{10}$,
 $C(O)C(O)R^{11}$, $OC(O)R^{11}$, $COOR^{11}$, $C(O)SR^{11}$, $C(O)NR^{10}R^{10}$, $C(S)NR^{10}R^{10}$,
 $C(O)NR^{10}R^{11}$, $C(S)NR^{10}R^{11}$, $OC(O)NR^{10}R^{11}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)R^{11}$,
10 $NR^{10}C(S)R^{10}$, $NR^{10}C(S)R^{11}$, $NR^{10}C(O)NR^{10}R^{10}$, $NR^{10}C(O)NR^{10}R^{11}$,
 $NR^{10}C(S)NR^{10}R^{10}$, $NR^{10}C(S)NR^{10}R^{11}$, $NR^{10}(COOR^{10})$, $NR^{10}(COOR^{11})$,
 $NR^{10}C(O)C(O)R^{10}$, $NR^{10}C(O)C(O)R^{11}$, $NR^{10}C(O)C(O)NR^{10}R^{11}$, $S(O)_2R^{10}$,
 $S(O)_2R^{11}$, $S(O)_2NR^{10}R^{10}$, $S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2R^{10}$
or $NR^{10}S(O)_2R^{11}$;
- 15 R^3 is H, halo, haloalkyl, NO_2 , CN, OR^7 , SR^7 , NR^7R^8 ,
 $C(O)R^7$, $COOR^7$, $C(O)NR^7R^7$, $C(O)NR^7R^8$, $NR^7C(O)NR^7R^7$, $NR^7C(O)NR^7R^8$,
 $OC(O)NR^7R^8$, $S(O)_2R^7$, $S(O)_2NR^7R^7$, $S(O)_2NR^7R^8$, $NR^7S(O)_2R^7$,
 $NR^7S(O)_2R^8$, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -
cycloalkyl or C_{4-10} -cycloalkenyl, each of the C_{1-10} -alkyl, C_{2-}
20 $_{10}$ -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl and C_{4-10} -
cycloalkenyl optionally comprising 1-4 heteroatoms selected
from N, O and S and optionally substituted with 1-5
substituents of R^8 or R^9 ;
- alternatively R^1 and R^3 taken together with the atoms to
25 which they are attached form a partially or fully
unsaturated 5- or 6-membered ring of carbon atoms optionally
including 1-3 heteroatoms selected from O, N, or S, and the
ring optionally substituted independently with 1-3
substituents of R^8 or R^9 ;
- 30 R^4 is H, halo, haloalkyl, NO_2 , CN, NR^7R^7 , OR^7 ; SR^7 ,
 $C(O)R^7$, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -
cycloalkyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -
alkynyl and C_{3-10} -cycloalkyl optionally comprising 1-4

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heteroatoms selected from N, O and S and optionally substituted with 1-5 substituents of R⁹;

alternatively R³ and R⁴ taken together with the atoms to which they are attached form a partially or fully
5 unsaturated 5- or 6-membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-3 substituents of R⁸ or R⁹

R⁵ is H, halo, haloalkyl, NO₂, CN, NR⁷R⁷, OR⁷; SR⁷,
10 C(O)R⁷, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-cycloalkyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl and C₃₋₁₀-cycloalkyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-5 substituents of R⁹;

15 R⁶ is H, halo, haloalkyl, NO₂, CN, SR⁷, OR⁷, C(O)R⁷, COOR⁷, OC(O)R⁷, NR⁷R⁷, NR⁷R⁸, C(O)NR⁷R⁷, C(O)NR⁷R⁸, NR⁷C(O)R⁷, NR⁷C(O)NR⁷R⁸, S(O)NR⁷R⁸, S(O)₂NR⁷R⁸, NR⁷S(O)NR⁷R⁸, NR⁷S(O)₂NR⁷R⁸, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl or C₄₋₁₀-cycloalkenyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl and C₄₋₁₀-cycloalkenyl optionally
20 comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-5 substituents of R⁸ or R⁹;

alternatively R¹ and R⁶ taken together with the atoms to which they are attached form a partially or fully
25 unsaturated 5- or 6-membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-5 substituents of R⁸ or R⁹;

alternatively R⁵ and R⁶ taken together with the atoms to
30 which they are attached form a partially or fully unsaturated 5- or 6-membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-3 substituents of R⁸ or R⁹;

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R⁷ is H, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl or C₄₋₁₀-cycloalkenyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl and C₄₋₁₀-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-5 substituents of NR⁸R⁹, NR⁹R⁹, OR⁸, SR⁸, OR⁹, SR⁹, C(O)R⁸, OC(O)R⁸, COOR⁸, C(O)R⁹, OC(O)R⁹, COOR⁹, C(O)NR⁸R⁹, C(O)NR⁹R⁹, NR⁹C(O)R⁸, NR⁹C(O)R⁹, NR⁹C(O)NR⁸R⁹, NR⁹C(O)NR⁹R⁹, NR⁹(COOR⁸), NR⁹(COOR⁹), OC(O)NR⁸R⁹, OC(O)NR⁹R⁹, S(O)₂R⁸, S(O)₂NR⁸R⁹, S(O)₂R⁹, S(O)₂NR⁹R⁹, NR⁹S(O)₂NR⁸R⁹, NR⁹S(O)₂NR⁹R⁹, NR⁹S(O)₂R⁸, NR⁹S(O)₂R⁹, R⁸ or R⁹;

R⁸ is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein said ring system is optionally substituted independently with 1-5 substituents of R⁹, oxo, NR⁹R⁹, OR⁹, SR⁹, C(O)R⁹ or a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of R⁹;

alternatively, R⁷ and R⁸ taken together form a saturated or partially or fully unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and said ring optionally substituted independently with 1-5 substituents of R⁹;

R⁹ is H, halo, haloalkyl, CN, OH, NO₂, NH₂, acetyl, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl or a saturated or partially or fully unsaturated 5-8 membered monocyclic or a 6-12 membered bicyclic, said ring system formed of carbon atoms optionally

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including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, wherein each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl and ring of said ring system is optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamine, dimethylamine, ethylamine, diethylamine, propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;

R¹⁰ is H, halo, haloalkyl, CN, NO₂, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl or C₄₋₁₀-cycloalkenyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl and C₄₋₁₀-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-5 substituents of R¹¹, R¹² or R¹⁶, NR¹¹R¹², NR¹²R¹², OR¹¹, SR¹¹, OR¹², SR¹², C(O)R¹¹, OC(O)R¹¹, COOR¹¹, C(O)R¹², OC(O)R¹², COOR¹², C(O)NR¹¹R¹², NR¹²C(O)R¹¹, C(O)NR¹²R¹², NR¹²C(O)R¹², NR¹²C(O)NR¹¹R¹², NR¹²C(O)NR¹²R¹², NR¹²(COOR¹¹), NR¹²(COOR¹²), OC(O)NR¹¹R¹², OC(O)NR¹²R¹², S(O)₂R¹¹, S(O)₂R¹², S(O)₂NR¹¹R¹², S(O)₂NR¹²R¹², NR¹²S(O)₂NR¹¹R¹², NR¹²S(O)₂NR¹²R¹², NR¹²S(O)₂R¹¹, NR¹²S(O)₂R¹², NR¹²S(O)₂R¹¹ or NR¹²S(O)₂R¹²;

R¹¹ is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein each ring of said ring system is optionally substituted independently with 1-5 substituents of R¹², R¹³, R¹⁴ or R¹⁶;

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alternatively, R^{10} and R^{11} taken together form a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-5 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which is optionally substituted independently with 1-5 substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} , SR^{14} , OR^{15} , SR^{15} , $C(O)R^{14}$, $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$, $C(O)NR^{15}R^{15}$, $NR^{14}C(O)R^{14}$, $NR^{15}C(O)R^{14}$, $NR^{14}C(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(O)NR^{14}R^{15}$, $NR^{15}C(O)NR^{15}R^{15}$, $NR^{15}(COOR^{14})$, $NR^{15}(COOR^{15})$, $OC(O)NR^{14}R^{15}$, $OC(O)NR^{15}R^{15}$, $S(O)_2R^{14}$, $S(O)_2R^{15}$, $S(O)_2NR^{14}R^{15}$, $S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2NR^{14}R^{15}$, $NR^{15}S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2R^{14}$ or $NR^{15}S(O)_2R^{15}$;

R^{14} is a partially or fully saturated or unsaturated 5-8 membered or a saturated or partially or fully unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein said ring system is optionally substituted independently with 1-5 substituents of R^{15} or R^{16} ;

R^{15} is H or C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkoxyl, each of which is optionally substituted independently with 1-5 substituents of R^{16} ;

R^{16} is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl,

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cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl; and provided that (1) when said at least one substituent on said R² ring system is C(O)NR¹⁰R¹⁰ or C(O)NR¹⁰R¹¹, then R¹⁰ and R¹¹, independently, are not -CH₂-L-Q or -C(C₁₋₆alkyl)(C₁₋₆alkyl)-L-Q, wherein L is -O-, -NH-, -NHC(O)-, -NHC(O)N-, -NHC(=NH)N- or -CO₂- and Q is H, substituted or unsubstituted C₁₋₆alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteraryl or C₁₋₆alkyl substituted with aryl, heterocyclyl or heteroaryl; or (2) when said R² is a phenyl ring substituted with C(O)NR¹⁰R¹⁰ or C(O)NR¹⁰R¹¹ meta to the alkynyl group of Formula I, then either (a) R¹ is not halogen, C₁₋₆alkyl, C₁₋₆alkoxyl or hydroxyl or (b) where R¹ and R³ taken together with the atoms to which they are attached form a partially or fully unsaturated 5- or 6-membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, said ring is not substituted with halogen, C₁₋₆alkyl, C₁₋₆alkoxyl or hydroxyl substituents.

2. The compound of Claim 1 wherein A¹ is N, A² is CR⁴, A³ is CR⁵ and A⁴ is CR⁶.

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3. The compound of Claim 1 wherein A^1 is CR^3 , A^2 is CR^4 , A^3 is CR^5 and A^4 is N.
- 5 4. The compound of Claim 1 wherein each of A^2 and A^3 , independently, is N, A^1 is CR^3 and A^4 is CR^6 .
5. The compound of Claim 1 wherein each of A^1 and A^2 , independently, is N, A^3 is CR^5 and A^4 is CR^6 .
- 10 6. The compound of Claim 1 wherein each of A^1 and A^4 , independently, is N, A^2 is CR^4 and A^3 is CR^5 .
7. The compound of Claim 6 wherein R^2 is a phenyl, naphthyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl ring system and one substituent on R^2 is
- 15 C(O) R^{10} , COO R^{10} , C(O) R^{11} , COO R^{11} , C(O)NR $^{10}R^{10}$, C(S)NR $^{10}R^{10}$, C(O)NR $^{10}R^{11}$, C(S)NR $^{10}R^{11}$, NR 10 C(O) R^{10} , NR 10 C(S) R^{10} , NR 10 C(O) R^{11} , NR 10 C(S) R^{11} , NR 10 C(O)NR $^{10}R^{10}$, NR 10 C(O)NR $^{10}R^{11}$, NR 10 C(S)NR $^{10}R^{10}$, NR 10 C(S)NR $^{10}R^{11}$, NR 10 (COO R^{10}), NR 10 (COO R^{11}), S(O) $_2$ NR $^{10}R^{10}$, S(O) $_2$ NR $^{10}R^{11}$, NR 10 S(O) $_2$ NR $^{10}R^{11}$, NR 10 S(O) $_2R^{10}$ or NR 10 S(O) $_2R^{11}$.
- 25 8. The compound of Claim 1 wherein
 A^1 and A^4 , independently, are N;
 A^2 is CR^4 ;
 A^3 is CR^5 ;
- 30 R^1 is NR $^7R^7$, NR $^7R^8$, SR 7 , OR 8 , SR 8 , C(O) R^7 , OC(O) R^7 , COO R^7 , C(O) R^8 , OC(O) R^8 , COO R^8 , C(O)NR $^7R^7$, C(S)NR $^7R^7$, NR 7 C(O) R^7 , NR 7 C(S) R^7 , NR 7 C(O)NR $^7R^7$, NR 7 C(S)NR $^7R^7$, NR 7 (COO R^7), OC(O)NR $^7R^7$, C(O)NR $^7R^8$, C(S)NR $^7R^8$, NR 7 C(O) R^8 , NR 7 C(S) R^8 , NR 7 C(O)NR $^7R^8$, NR 7 C(S)NR $^7R^8$, NR 7 (COO R^8), OC(O)NR $^7R^8$, S(O) $_2R^7$, S(O) $_2$ NR $^7R^7$,

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$\text{NR}^7\text{S}(\text{O})_2\text{NR}^7\text{R}^7$, $\text{NR}^7\text{S}(\text{O})_2\text{R}^7$, $\text{S}(\text{O})_2\text{R}^8$, $\text{S}(\text{O})_2\text{NR}^7\text{R}^8$, $\text{NR}^7\text{S}(\text{O})_2\text{NR}^7\text{R}^8$ or $\text{NR}^7\text{S}(\text{O})_2\text{R}^8$;

- R^2 is a phenyl, naphthyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, phthalazinyl, aza-phthalazinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, thiadiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl ring system, said ring system substituted independently with 1-5 substituents of R^{10} , R^{11} , R^{15} , $\text{NR}^{10}\text{R}^{10}$, $\text{NR}^{10}\text{R}^{11}$, OR^{10} , SR^{10} , OR^{11} , SR^{11} , $\text{C}(\text{O})\text{R}^{10}$, $\text{C}(\text{S})\text{R}^{10}$, $\text{C}(\text{NCN})\text{R}^{10}$, $\text{C}(\text{O})\text{R}^{11}$, $\text{C}(\text{S})\text{R}^{11}$, $\text{C}(\text{NCN})\text{R}^{11}$, $\text{C}(\text{O})\text{C}(\text{O})\text{R}^{10}$, $\text{OC}(\text{O})\text{R}^{10}$, COOR^{10} , $\text{C}(\text{O})\text{SR}^{10}$, $\text{C}(\text{O})\text{C}(\text{O})\text{R}^{11}$, $\text{OC}(\text{O})\text{R}^{11}$, COOR^{11} , $\text{C}(\text{O})\text{SR}^{11}$, $\text{C}(\text{O})\text{NR}^{10}\text{R}^{10}$, $\text{C}(\text{S})\text{NR}^{10}\text{R}^{10}$, $\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$, $\text{C}(\text{S})\text{NR}^{10}\text{R}^{11}$, $\text{OC}(\text{O})\text{NR}^{10}\text{R}^{11}$, $\text{NR}^{10}\text{C}(\text{O})\text{R}^{10}$, $\text{NR}^{10}\text{C}(\text{O})\text{R}^{11}$, $\text{NR}^{10}\text{C}(\text{S})\text{R}^{10}$, $\text{NR}^{10}\text{C}(\text{S})\text{R}^{11}$, $\text{NR}^{10}\text{C}(\text{O})\text{NR}^{10}\text{R}^{10}$, $\text{NR}^{10}\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$, $\text{NR}^{10}\text{C}(\text{S})\text{NR}^{10}\text{R}^{10}$, $\text{NR}^{10}\text{C}(\text{S})\text{NR}^{10}\text{R}^{11}$, $\text{NR}^{10}(\text{COOR}^{10})$, $\text{NR}^{10}(\text{COOR}^{11})$, $\text{NR}^{10}\text{C}(\text{O})\text{C}(\text{O})\text{R}^{10}$, $\text{NR}^{10}\text{C}(\text{O})\text{C}(\text{O})\text{R}^{11}$, $\text{NR}^{10}\text{C}(\text{O})\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$, $\text{S}(\text{O})_2\text{R}^{10}$, $\text{S}(\text{O})_2\text{R}^{11}$, $\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{10}$, $\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{11}$, $\text{NR}^{10}\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{11}$, $\text{NR}^{10}\text{S}(\text{O})_2\text{R}^{10}$ or $\text{NR}^{10}\text{S}(\text{O})_2\text{R}^{11}$, provided that (1) one substituent is $\text{C}(\text{O})\text{R}^{10}$, COOR^{10} , $\text{C}(\text{O})\text{R}^{11}$, COOR^{11} , $\text{C}(\text{O})\text{NR}^{10}\text{R}^{10}$, $\text{C}(\text{S})\text{NR}^{10}\text{R}^{10}$, $\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$, $\text{C}(\text{S})\text{NR}^{10}\text{R}^{11}$, $\text{NR}^{10}\text{C}(\text{O})\text{R}^{10}$, $\text{NR}^{10}\text{C}(\text{S})\text{R}^{10}$, $\text{NR}^{10}\text{C}(\text{O})\text{R}^{11}$, $\text{NR}^{10}\text{C}(\text{S})\text{R}^{11}$, $\text{NR}^{10}\text{C}(\text{S})\text{NR}^{10}\text{R}^{10}$, $\text{NR}^{10}\text{C}(\text{S})\text{NR}^{10}\text{R}^{11}$, $\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{10}$, $\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{11}$, $\text{NR}^{10}\text{S}(\text{O})_2\text{NR}^{10}\text{R}^{11}$, $\text{NR}^{10}\text{S}(\text{O})_2\text{R}^{10}$ or $\text{NR}^{10}\text{S}(\text{O})_2\text{R}^{11}$;

- R^4 is H, halo, haloalkyl, NO_2 , CN, NR^7R^7 , OR^7 , SR^7 , $\text{C}(\text{O})\text{R}^7$, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl and C_{3-10} -cycloalkyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-3 substituents of R^9 ;

R^5 is H, halo, haloalkyl, NO_2 , CN, NR^7R^7 , OR^7 , SR^7 , $\text{C}(\text{O})\text{R}^7$, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -

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alkynyl and C₃₋₁₀-cycloalkyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-3 substituents of R⁹;

R⁷ is H, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl or C₄₋₁₀-cycloalkenyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl and C₄₋₁₀-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-3 substituents of NR⁸R⁹, NR⁹R⁹, OR⁸, SR⁸, OR⁹, SR⁹, C(O)R⁸, OC(O)R⁸, COOR⁸, C(O)R⁹, OC(O)R⁹, COOR⁹, C(O)NR⁸R⁹, C(O)NR⁹R⁹, NR⁹C(O)R⁸, NR⁹C(O)R⁹, NR⁹C(O)NR⁸R⁹, NR⁹C(O)NR⁹R⁹, NR⁹(COOR⁸), NR⁹(COOR⁹), OC(O)NR⁸R⁹, OC(O)NR⁹R⁹, S(O)₂R⁸, S(O)₂NR⁸R⁹, S(O)₂R⁹, S(O)₂NR⁹R⁹, NR⁹S(O)₂NR⁸R⁹, NR⁹S(O)₂NR⁹R⁹, NR⁹S(O)₂R⁸, NR⁹S(O)₂R⁹, R⁸ or R⁹;

R⁸ is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein said ring system is optionally substituted independently with 1-5 substituents of R⁹, oxo, NR⁹R⁹, OR⁹, SR⁹, C(O)R⁹ or a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and optionally substituted independently with 1-3 substituents of R⁹;

alternatively, R⁷ and R⁸ taken together form a saturated or partially or fully unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-3 substituents of R⁹;

R⁹ is H, halo, haloalkyl, CN, OH, NO₂, NH₂, acetyl, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-

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alkoxyl, C₁₋₁₀-thioalkoxyl or a saturated or partially or fully unsaturated 5-8 membered monocyclic or a 6-12 membered bicyclic, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, wherein each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl and ring of said ring system is optionally substituted independently with 1-3 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamine, dimethylamine, ethylamine, diethylamine, propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;

R¹⁰ is H, halo, haloalkyl, CN, NO₂, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl or C₄₋₁₀-cycloalkenyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl and C₄₋₁₀-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-5 substituents of R¹¹, R¹² or R¹⁶, NR¹¹R¹², NR¹²R¹², OR¹¹, SR¹¹, OR¹², SR¹², C(O)R¹¹, OC(O)R¹¹, COOR¹¹, C(O)R¹², OC(O)R¹², COOR¹², C(O)NR¹¹R¹², NR¹²C(O)R¹¹, C(O)NR¹²R¹², NR¹²C(O)R¹², NR¹²C(O)NR¹¹R¹², NR¹²C(O)NR¹²R¹², NR¹²(COOR¹¹), NR¹²(COOR¹²), OC(O)NR¹¹R¹², OC(O)NR¹²R¹², S(O)₂R¹¹, S(O)₂R¹², S(O)₂NR¹¹R¹², S(O)₂NR¹²R¹², NR¹²S(O)₂NR¹¹R¹², NR¹²S(O)₂NR¹²R¹², NR¹²S(O)₂R¹¹, NR¹²S(O)₂R¹², NR¹²S(O)₂R¹¹ or NR¹²S(O)₂R¹²;

R¹¹ is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein each ring of said ring system is optionally

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substituted independently with 1-5 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

alternatively, R^{10} and R^{11} taken together form a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-5 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which is optionally substituted independently with 1-5 substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} , SR^{14} , OR^{15} , SR^{15} , $C(O)R^{14}$, $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$, $C(O)NR^{15}R^{15}$, $NR^{14}C(O)R^{14}$, $NR^{15}C(O)R^{14}$, $NR^{14}C(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(O)NR^{14}R^{15}$, $NR^{15}C(O)NR^{15}R^{15}$, $NR^{15}(COOR^{14})$, $NR^{15}(COOR^{15})$, $OC(O)NR^{14}R^{15}$, $OC(O)NR^{15}R^{15}$, $S(O)_2R^{14}$, $S(O)_2R^{15}$, $S(O)_2NR^{14}R^{15}$, $S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2NR^{14}R^{15}$, $NR^{15}S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2R^{14}$ or $NR^{15}S(O)_2R^{15}$;

R^{14} is a partially or fully saturated or unsaturated 5-8 membered or a saturated or partially or fully unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein each ring of said ring system is optionally substituted independently with 1-5 substituents of R^{15} or R^{16} ;

R^{15} is H or C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkoxyl, each of

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which is optionally substituted independently with 1-5 substituents of R^{16} ;

R^{16} is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO_2 , NH_2 , OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl;

and provided that (1) when said at least one substituent on said R^2 ring system is $C(O)NR^{10}R^{10}$ or $C(O)NR^{10}R^{11}$, then R^{10} and R^{11} , independently, are not $-CH_2-L-Q$ or $-C(C_{1-6}alkyl)(C_{1-6}alkyl)-L-Q$, wherein L is $-O-$, $-NH-$, $-NHC(O)-$, $-NHC(O)N-$, $-NHC(=NH)N-$ or $-CO_2-$ and Q is H, substituted or unsubstituted $C_{1-6}alkyl$, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteraryl or $C_{1-6}alkyl$ substituted with aryl, heterocyclyl or heteroaryl;

(2) where the sole substituent on said R^2 ring system is R^{10} , said substituent is not $C_1-alkyl-C(O)NR^{11}R^{12}$, $C_1-alkyl-NR^{12}C(O)R^{11}$, $C_1-alkyl-C(O)NR^{12}R^{12}$ or $C_1-alkyl-NR^{12}C(O)R^{12}$, wherein the $C_1-alkyl$ portion is CH_2 or substituted with $C_{1-6}alkyl$ or cycloalkyl; or

(3) when said R^2 is a phenyl ring substituted with $C(O)NR^{10}R^{10}$ or $C(O)NR^{10}R^{11}$ meta to the point of attachment of the alkynyl group on R^2 of Formula I, then either (a) R^1 is

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not halogen, C₁₋₆alkyl, C₁₋₆alkoxyl or hydroxyl or (b) where R¹ and R³ taken together with the atoms to which they are attached form a partially or fully unsaturated 5- or 6-membered ring of carbon atoms optionally including 1-3
 5 heteroatoms selected from O, N, or S, said ring is not substituted with halogen, C₁₋₆alkyl, C₁₋₆alkoxyl or hydroxyl substituents.

9. The compound of Claim 8 wherein
- 10 R¹ is R⁷, NR⁷R⁷, NR⁷R⁸, SR⁷, C(O)R⁷, C(O)NR⁷R⁷, C(S)NR⁷R⁷, NR⁷C(O)R⁷, NR⁷C(S)R⁷, NR⁷C(O)NR⁷R⁷, NR⁷C(S)NR⁷R⁷, NR⁷(COOR⁷), C(O)NR⁷R⁸, C(S)NR⁷R⁸, NR⁷C(O)NR⁷R⁸, NR⁷C(S)NR⁷R⁸, S(O)₂R⁷, S(O)₂NR⁷R⁷, NR⁷S(O)₂NR⁷R⁷, NR⁷S(O)₂R⁷, S(O)₂NR⁷R⁸ or NR⁷S(O)₂NR⁷R⁸;
- 15 R² is a phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl ring system, said ring system substituted independently with 1-3 substituents of R¹⁰, R¹¹, R¹⁵, NR¹⁰R¹⁰, NR¹⁰R¹¹, OR¹⁰, SR¹⁰, OR¹¹, SR¹¹, C(O)R¹⁰, C(S)R¹⁰, C(NCN)R¹⁰, C(O)R¹¹, C(S)R¹¹, C(NCN)R¹¹, C(O)C(O)R¹⁰, OC(O)R¹⁰, COOR¹⁰, C(O)SR¹⁰, C(O)C(O)R¹¹, OC(O)R¹¹, COOR¹¹,
 25 C(O)SR¹¹, C(O)NR¹⁰R¹⁰, C(S)NR¹⁰R¹⁰, C(O)NR¹⁰R¹¹, C(S)NR¹⁰R¹¹, OC(O)NR¹⁰R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(O)R¹¹, NR¹⁰C(S)R¹⁰, NR¹⁰C(S)R¹¹, NR¹⁰C(O)NR¹⁰R¹⁰, NR¹⁰C(O)NR¹⁰R¹¹, NR¹⁰C(S)NR¹⁰R¹⁰, NR¹⁰C(S)NR¹⁰R¹¹, NR¹⁰(COOR¹⁰), NR¹⁰(COOR¹¹), NR¹⁰C(O)C(O)R¹⁰, NR¹⁰C(O)C(O)R¹¹, NR¹⁰C(O)C(O)NR¹⁰R¹¹, S(O)₂R¹⁰, S(O)₂R¹¹, S(O)₂NR¹⁰R¹⁰, S(O)₂NR¹⁰R¹¹,
 30 NR¹⁰S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂R¹⁰ or NR¹⁰S(O)₂R¹¹, provided that one substituent is C(O)R¹¹, COOR¹¹, C(O)NR¹⁰R¹¹, C(S)NR¹⁰R¹¹, NR¹⁰C(O)R¹¹, NR¹⁰C(S)R¹¹, NR¹⁰C(O)NR¹⁰R¹¹, NR¹⁰C(S)NR¹⁰R¹¹, NR¹⁰(COOR¹¹), S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂NR¹⁰R¹¹ or NR¹⁰S(O)₂R¹¹;

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R⁴ is H, halo, haloalkyl, NO₂, CN, NH₂, N-C₁₋₁₀-alkyl, N-C₁₋₁₀-dialkyl, O-C₁₋₁₀-alkyl, S-C₁₋₁₀-alkyl, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-cycloalkyl;

R⁵ is H, halo, haloalkyl, NO₂, CN, NH₂, N-C₁₋₁₀-alkyl, N-C₁₋₁₀-dialkyl, O-C₁₋₁₀-alkyl, S-C₁₋₁₀-alkyl, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-cycloalkyl;

R⁷ is H, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-cycloalkyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl and C₃₋₁₀-cycloalkyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-3 substituents of NR⁸R⁹, NR⁹R⁹, OR⁸, SR⁸, OR⁹, SR⁹, C(O)R⁸, OC(O)R⁸, COOR⁸, C(O)R⁹, OC(O)R⁹, COOR⁹, C(O)NR⁸R⁹, C(O)NR⁹R⁹, NR⁹C(O)R⁸, NR⁹C(O)R⁹, NR⁹C(O)NR⁸R⁹, NR⁹C(O)NR⁹R⁹, NR⁹(COOR⁸), NR⁹(COOR⁹), OC(O)NR⁸R⁹, OC(O)NR⁹R⁹, S(O)₂R⁸, S(O)₂NR⁸R⁹, S(O)₂R⁹, S(O)₂NR⁹R⁹, NR⁹S(O)₂NR⁸R⁹, NR⁹S(O)₂NR⁹R⁹, NR⁹S(O)₂R⁸, NR⁹S(O)₂R⁹, R⁸ or R⁹;

R⁸ is a ring system of phenyl, naphthyl, pyridyl, pyrimidinyl, pyrrolidinyl, piperidinyl, piperazinyl, triazinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, tetrahydroquinazolinyl, tetrahydroisoquinazolinyl, morpholinyl, thiophenyl, furyl, dihydrofuryl, tetrahydrofuryl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl, said ring system optionally substituted independently with 1-3 substituents of R⁹, oxo, NR⁹R⁹, OR⁹, SR⁹, C(O)R⁹ or a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and optionally substituted independently with 1-3 substituents of R⁹;

alternatively, R⁷ and R⁸ taken together form a saturated or partially or fully unsaturated 5-6 membered

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ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-3 substituents of R⁹;

- R⁹ is H, halo, haloalkyl, CN, OH, NO₂, NH₂, acetyl, C₁-
 5 ₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₁₋₁₀-
 alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-
 thioalkoxyl or a ring system of phenyl, naphthyl, pyridyl,
 pyrimidinyl, pyrrolidinyl, piperidinyl, piperazinyl,
 quinolinyl, isoquinolinyl, tetrahydroquinolinyl,
 10 tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl,
 tetrahydroquinazolinyl, tetrahydroisoquinazolinyl,
 morpholinyl, thiophenyl, furyl, dihydrofuryl,
 tetrahydrofuryl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl,
 isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl,
 15 benzofuranyl, dihydrobenzofuranyl, benzothiophenyl and
 benzimidazolyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-
 alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-
 , C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl and ring
 system optionally substituted independently with 1-3
 20 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, oxo,
 methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl,
 isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl,
 methylamine, dimethylamine, ethylamine, diethylamine,
 propylamine, isopropylamine, dipropylamine,
 25 diisopropylamine, benzyl or phenyl;

- R¹⁰ is H, halo, haloalkyl, CN, NO₂, C₁₋₁₀-alkyl, C₂₋₁₀-
 alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl or C₄₋₁₀-cycloalkenyl,
 each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-
 cycloalkyl and C₄₋₁₀-cycloalkenyl optionally comprising 1-4
 30 heteroatoms selected from N, O and S and optionally
 substituted with 1-5 substituents of R¹¹, R¹² or R¹⁶, NR¹¹R¹²,
 NR¹²R¹², OR¹¹, SR¹¹, OR¹², SR¹², C(O)R¹¹, OC(O)R¹¹, COOR¹¹,
 C(O)R¹², OC(O)R¹², COOR¹², C(O)NR¹¹R¹², NR¹²C(O)R¹¹, C(O)NR¹²R¹²,
 NR¹²C(O)R¹², NR¹²C(O)NR¹¹R¹², NR¹²C(O)NR¹²R¹², NR¹²(COOR¹¹),

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$\text{NR}^{12}(\text{COOR}^{12})$, $\text{OC}(\text{O})\text{NR}^{11}\text{R}^{12}$, $\text{OC}(\text{O})\text{NR}^{12}\text{R}^{12}$, $\text{S}(\text{O})_2\text{R}^{11}$, $\text{S}(\text{O})_2\text{R}^{12}$,
 $\text{S}(\text{O})_2\text{NR}^{11}\text{R}^{12}$, $\text{S}(\text{O})_2\text{NR}^{12}\text{R}^{12}$, $\text{NR}^{12}\text{S}(\text{O})_2\text{NR}^{11}\text{R}^{12}$, $\text{NR}^{12}\text{S}(\text{O})_2\text{NR}^{12}\text{R}^{12}$,
 $\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{11}$, $\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{12}$, $\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{11}$ or $\text{NR}^{12}\text{S}(\text{O})_2\text{R}^{12}$;

R^{11} is a ring system of phenyl, naphthyl, pyridyl,
 5 pyrimidinyl, triazinyl, quinolinyl, isoquinolinyl,
 tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinazolinyl,
 isoquinazolinyl, tetrahydroquinazolinyl,
 tetrahydroisoquinazolinyl, morpholinyl, thiophenyl, furyl,
 dihydrofuryl, tetrahydrofuryl, pyrrolyl, imidazolyl,
 10 triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl,
 indolyl, isoindolyl, indolinyl, benzofuranyl,
 dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl, said
 ring system optionally substituted independently with 1-5
 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

15 alternatively, R^{10} and R^{11} taken together form a
 partially or fully saturated or unsaturated 5-6 membered
 ring of carbon atoms optionally including 1-3 heteroatoms
 selected from O, N, or S, and the ring optionally
 substituted independently with 1-5 substituents of R^{12} , R^{13} ,
 20 R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -
 cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -
 dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which
 is optionally substituted independently with 1-5
 25 substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

R^{13} is $\text{NR}^{14}\text{R}^{15}$, $\text{NR}^{15}\text{R}^{15}$, OR^{14} , SR^{14} , OR^{15} , SR^{15} , $\text{C}(\text{O})\text{R}^{14}$,
 $\text{OC}(\text{O})\text{R}^{14}$, COOR^{14} , $\text{C}(\text{O})\text{R}^{15}$, $\text{OC}(\text{O})\text{R}^{15}$, COOR^{15} , $\text{C}(\text{O})\text{NR}^{14}\text{R}^{15}$,
 $\text{C}(\text{O})\text{NR}^{15}\text{R}^{15}$, $\text{NR}^{14}\text{C}(\text{O})\text{R}^{14}$, $\text{NR}^{15}\text{C}(\text{O})\text{R}^{14}$, $\text{NR}^{14}\text{C}(\text{O})\text{R}^{15}$, $\text{NR}^{15}\text{C}(\text{O})\text{R}^{15}$,
 $\text{NR}^{15}\text{C}(\text{O})\text{NR}^{14}\text{R}^{15}$, $\text{NR}^{15}\text{C}(\text{O})\text{NR}^{15}\text{R}^{15}$, $\text{NR}^{15}(\text{COOR}^{14})$, $\text{NR}^{15}(\text{COOR}^{15})$,
 30 $\text{OC}(\text{O})\text{NR}^{14}\text{R}^{15}$, $\text{OC}(\text{O})\text{NR}^{15}\text{R}^{15}$, $\text{S}(\text{O})_2\text{R}^{14}$, $\text{S}(\text{O})_2\text{R}^{15}$, $\text{S}(\text{O})_2\text{NR}^{14}\text{R}^{15}$,
 $\text{S}(\text{O})_2\text{NR}^{15}\text{R}^{15}$, $\text{NR}^{14}\text{S}(\text{O})_2\text{NR}^{14}\text{R}^{15}$, $\text{NR}^{15}\text{S}(\text{O})_2\text{NR}^{15}\text{R}^{15}$, $\text{NR}^{14}\text{S}(\text{O})_2\text{R}^{14}$ or
 $\text{NR}^{15}\text{S}(\text{O})_2\text{R}^{15}$;

R^{14} is a partially or fully saturated or unsaturated 5-
 8 membered or a saturated or partially or fully unsaturated

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5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein each ring of said ring system is optionally substituted independently with 1-5 substituents of R¹⁵ or R¹⁶;

R¹⁵ is H or C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl or C₁₋₁₀-thioalkoxyl, each of which is optionally substituted independently with 1-5 substituents of R¹⁶; and

R¹⁶ is H, halo, haloalkyl, CN, OH, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

10. The compound of Claim 9 wherein R¹ is NH₂ or NCH₃.

11. The compound of Claim 8 wherein

A² is CH;

A³ is CH;

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R^1 is NR^7R^7 , NR^7R^8 , SR^7 , $C(O)R^7$, $COOR^7$, $C(O)NR^7R^7$, $NR^7C(O)R^7$, $NR^7C(O)NR^7R^7$, $NR^7(COOR^7)$, $C(O)NR^7R^8$, $NR^7C(O)R^8$, $NR^7C(O)NR^7R^8$, $NR^7(COOR^8)$, $S(O)_2R^7$, $S(O)_2NR^7R^7$, $NR^7S(O)_2NR^7R^7$, $NR^7S(O)_2R^7$, $S(O)_2NR^7R^8$, $NR^7S(O)_2NR^7R^8$ or $NR^7S(O)_2R^8$;

- 5 R^2 is a phenyl, naphthyl, pyridyl, pyrimidinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl ring system, said ring system substituted independently with 1-3 substituents of R^{10} , R^{11} , R^{15} , $NR^{10}R^{10}$, $NR^{10}R^{11}$, OR^{10} , SR^{10} , OR^{11} , SR^{11} , $C(O)R^{10}$, $C(S)R^{10}$, $C(NCN)R^{10}$, $C(O)R^{11}$, $C(S)R^{11}$, $C(NCN)R^{11}$, $C(O)C(O)R^{10}$, $OC(O)R^{10}$, $COOR^{10}$, $C(O)SR^{10}$, $C(O)C(O)R^{11}$, $OC(O)R^{11}$, $COOR^{11}$, $C(O)SR^{11}$, $C(O)NR^{10}R^{10}$, $C(S)NR^{10}R^{10}$, $C(O)NR^{10}R^{11}$, $C(S)NR^{10}R^{11}$, $OC(O)NR^{10}R^{11}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)R^{11}$, $NR^{10}C(S)R^{10}$, $NR^{10}C(S)R^{11}$, $NR^{10}C(O)NR^{10}R^{10}$, $NR^{10}C(O)NR^{10}R^{11}$, $NR^{10}C(S)NR^{10}R^{10}$, $NR^{10}C(S)NR^{10}R^{11}$, $NR^{10}(COOR^{10})$, $NR^{10}(COOR^{11})$, $NR^{10}C(O)C(O)R^{10}$, $NR^{10}C(O)C(O)R^{11}$, $NR^{10}C(O)C(O)NR^{10}R^{11}$, $S(O)_2R^{10}$, $S(O)_2R^{11}$, $S(O)_2NR^{10}R^{10}$, $S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2R^{10}$ or $NR^{10}S(O)_2R^{11}$, provided that one substituent is $C(O)NR^{10}R^{10}$, $C(S)NR^{10}R^{10}$, $C(O)NR^{10}R^{11}$, $C(S)NR^{10}R^{11}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(S)R^{10}$, $NR^{10}C(O)R^{11}$, $NR^{10}C(S)R^{11}$, $NR^{10}C(S)NR^{10}R^{10}$, $NR^{10}C(S)NR^{10}R^{11}$, $S(O)_2NR^{10}R^{10}$, $S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2R^{10}$ or $NR^{10}S(O)_2R^{11}$;

- 25 R^7 is H, C_{1-10} -alkyl or C_{3-10} -cycloalkyl, each of the C_{1-10} -alkyl and C_{3-10} -cycloalkyl optionally comprising 1-2 heteroatoms selected from N, O and S and optionally substituted with 1-3 substituents of R^9 ;

- 30 R^8 is a phenyl, naphthyl, pyridyl, pyrimidinyl, pyrrolidinyl, piperidinyl, piperazinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, tetrahydroquinazolinyl, tetrahydroisoquinazolinyl, morpholinyl, thiophenyl, furyl, dihydrofuryl,

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tetrahydrofuryl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl ring system, said ring system optionally
5 substituted independently with 1-3 substituents of R⁹, oxo, NR⁹R⁹, OR⁹; SR⁹, C(O)R⁹ or a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and optionally substituted independently with 1-3 substituents
10 of R⁹;

alternatively, R⁷ and R⁸ taken together form a 5-6 membered ring selected from pyrrolidine, piperidine, morpholine and piperazine, the ring optionally substituted independently with 1-3 substituents of R⁹;

15 R⁹ is H, halo, haloalkyl, CN, OH, NO₂, NH₂, acetyl, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl or a ring system of phenyl, naphthyl, pyridyl, pyrimidinyl, pyrrolidinyl, piperidinyl, piperazinyl,
20 quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, tetrahydroquinazolinyl, tetrahydroisoquinazolinyl, morpholinyl, thiophenyl, furyl, dihydrofuryl, tetrahydrofuryl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl,
25 isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl and benzimidazolyl, wherein each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl and ring system is optionally substituted
30 independently with 1-3 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamine, dimethylamine, ethylamine, diethylamine,

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propylamine, isopropylamine, dipropylamine,
diisopropylamine, benzyl or phenyl;

R^{10} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -
cycloalkyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -
5 alkynyl and C_{3-10} -cycloalkyl optionally comprising 1-4
heteroatoms selected from N, O and S and optionally
substituted with 1-3 substituents of R^{11} , R^{12} or R^{16} , $NR^{11}R^{12}$,
 $NR^{12}R^{12}$, OR^{11} , SR^{11} , OR^{12} , SR^{12} , $C(O)R^{11}$, $OC(O)R^{11}$, $COOR^{11}$,
 $C(O)R^{12}$, $OC(O)R^{12}$, $COOR^{12}$, $C(O)NR^{11}R^{12}$, $NR^{12}C(O)R^{11}$, $C(O)NR^{12}R^{12}$,
10 $NR^{12}C(O)R^{12}$, $NR^{12}C(O)NR^{11}R^{12}$, $NR^{12}C(O)NR^{12}R^{12}$, $NR^{12}(COOR^{11})$,
 $NR^{12}(COOR^{12})$, $OC(O)NR^{11}R^{12}$, $OC(O)NR^{12}R^{12}$, $S(O)_2R^{11}$, $S(O)_2R^{12}$,
 $S(O)_2NR^{11}R^{12}$, $S(O)_2NR^{12}R^{12}$, $NR^{12}S(O)_2NR^{11}R^{12}$, $NR^{12}S(O)_2NR^{12}R^{12}$,
 $NR^{12}S(O)_2R^{11}$, $NR^{12}S(O)_2R^{12}$, $NR^{12}S(O)_2R^{11}$ or $NR^{12}S(O)_2R^{12}$;

R^{11} is a phenyl, naphthyl, pyridyl, pyrimidinyl,
15 quinolinyl, isoquinolinyl, tetrahydroquinolinyl,
tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl,
tetrahydroquinazolinyl, tetrahydroisoquinazolinyl,
thiophenyl, furyl, pyrrolyl, imidazolyl, thiazolyl,
oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl,
20 indolinyl, benzofuranyl, dihydrobenzofuranyl,
benzothiophenyl or benzimidazolyl ring system, said ring
system optionally substituted independently with 1-3
substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

alternatively, R^{10} and R^{11} taken together form a
25 partially or fully saturated or unsaturated 5-6 membered
ring of carbon atoms optionally including 1-3 heteroatoms
selected from O, N, or S, said ring optionally substituted
independently with 1-3 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -
30 cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -
dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which
is optionally substituted independently with 1-3
substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

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R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} ; SR^{14} , OR^{15} ; SR^{15} , $C(O)R^{14}$, $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$, $C(O)NR^{15}R^{15}$, $NR^{14}C(O)R^{14}$, $NR^{15}C(O)R^{14}$, $NR^{14}C(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(O)NR^{14}R^{15}$, $NR^{15}C(O)NR^{15}R^{15}$, $NR^{15}(COOR^{14})$, $NR^{15}(COOR^{15})$,
 5 $OC(O)NR^{14}R^{15}$, $OC(O)NR^{15}R^{15}$, $S(O)_2R^{14}$, $S(O)_2R^{15}$, $S(O)_2NR^{14}R^{15}$, $S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2NR^{14}R^{15}$, $NR^{15}S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2R^{14}$ or $NR^{15}S(O)_2R^{15}$;

R^{14} is phenyl, naphthyl, pyridyl, pyrimidinyl, pyrrolidinyl, piperidinyl, piperazinyl, quinolinyl,
 10 isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, tetrahydroquinazolinyl, tetrahydroisoquinazolinyl, morpholinyl, thiophenyl, furyl, dihydrofuryl, tetrahydrofuryl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl,
 15 isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl, benzofuranyl, dihydrobenzofuranyl, benzoxazinyl, benzodioxazinyl, benzothiophenyl and benzimidazolyl, each of which is optionally substituted independently with 1-5 substituents of R^{15} or R^{16} ;

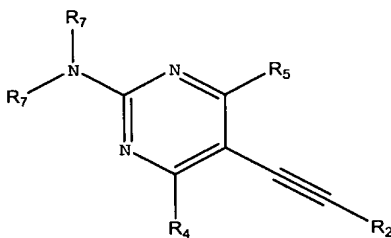
20 R^{15} is H or C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkoxyl, each of which is optionally substituted independently with 1-5 substituents of R^{16} ; and

25 R^{16} is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a
 30 partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally

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substituted independently with 1-5 substituents of halo,
haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl,
ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl,
isobutyl, tert-butyl, methylamino, dimethylamino,
5 ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

12. The compound of Claim 1, having a general Formula II

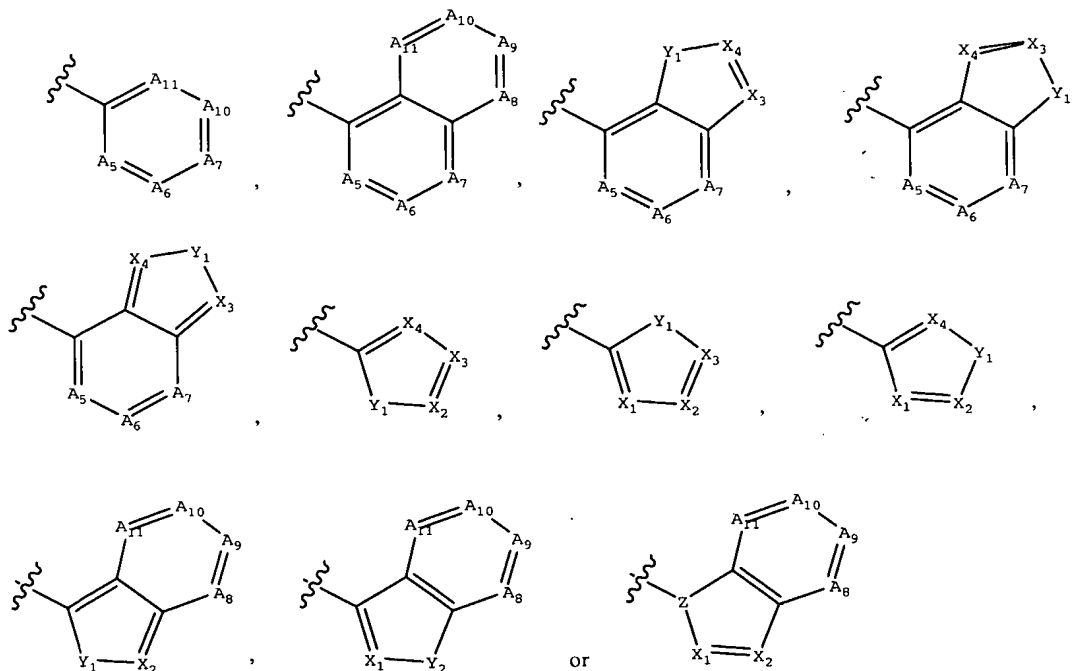


II

10

wherein

R² is



wherein

15

one of A⁶ and A⁷ is CR^{3a} and the other of A⁶ and A⁷
is CR^{3b} or N;

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each of A⁵, A⁸, A⁹, A¹⁰ and A¹¹ is, independently,
CR^{3b} or N;

X² is CR^{3a};

each of X¹, X³ and X⁴ is, independently, CR^{3b} or N;

5 Y¹ is CR^{3b}R^{3c}, NR^{3c}, O or S;

Y² is CR^{3a}R^{3b} or NR^{3a}; and

Z is CH or N;

R^{3a} is OC(O)R¹⁰, COOR¹⁰, OC(O)R¹¹, COOR¹¹, C(O)SR¹⁰,
C(O)SR¹¹, C(O)NR¹⁰R¹⁰, C(S)NR¹⁰R¹⁰, C(O)NR¹⁰R¹¹, C(S)NR¹⁰R¹¹,
10 NR¹⁰C(O)R¹⁰, NR¹⁰C(S)R¹⁰, NR¹⁰C(O)R¹¹, NR¹⁰C(S)R¹¹,
NR¹⁰C(S)NR¹⁰R¹⁰, NR¹⁰C(S)NR¹⁰R¹¹, OC(O)NR¹⁰R¹¹, S(O)₂R¹¹,
S(O)₂NR¹⁰R¹⁰, S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂R¹⁰ or
NR¹⁰S(O)₂R¹¹;

R^{3b} is H, halo, haloalkyl, CN, NO₂, NH₂, C₁₋₁₀-
15 alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-cycloalkyl;
and

R^{3c} is H, CN or C₁₋₁₀-alkyl;

R⁴ is H, halo, haloalkyl, NO₂, CN, OH, O-C₁₋₁₀-alkyl,
NH₂, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-
20 cycloalkyl;

R⁵ is H, halo, haloalkyl, NO₂, CN, OH, NH₂, O-C₁₋₁₀-
alkyl, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-
cycloalkyl;

Each R⁷, independently, is H, R⁸, C₁₋₁₀-alkyl, C₂₋₁₀-
25 alkenyl or C₂₋₁₀-alkynyl, each of which is optionally
substituted with 1-3 substituents of NR⁸R⁹, NR⁹R⁹, OR⁸, SR⁸,
OR⁹, SR⁹, C(O)R⁸, C(O)R⁹, C(O)NR⁸R⁹, C(O)NR⁹R⁹, S(O)₂R⁸,
S(O)₂NR⁸R⁹, S(O)₂R⁹, S(O)₂NR⁹R⁹, R⁸ or R⁹;

alternatively, NR⁷R⁷ form a 5-6 membered heterocyclic
30 ring selected from pyrrolidine, piperidine, morpholine and
piperazine, the ring optionally substituted independently
with 1-3 substituents of R⁹;

R⁸ is a ring system selected from phenyl, naphthyl,
pyridyl, piperazinyl, triazinyl, thiophenyl, furyl,

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pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, isoxazolinyl, thiazolinyl, 5 pyrazolinyl, morpholinyl, piperidinyl, pyranyl, dioxozinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, said ring system optionally substituted independently with 1-3 substituents of R⁹, oxo, NR⁹R⁹, OR⁹, SR⁹, C(O)R⁹, phenyl, pyridyl, piperidyl, piperazinyl, 10 morpholinyl or pyrrolidinyl;

R⁹ is H, halo, haloalkyl, CN, OH, NO₂, NH₂, acetyl, C₁-10-alkyl, C₂-10-alkenyl, C₂-10-alkynyl, C₃-10-cycloalkyl, C₄-10-cycloalkenyl, C₁-10-alkylamino-, C₁-10-dialkylamino-, C₁-10-alkoxyl, C₁-10-thioalkoxyl or a ring system selected from 15 phenyl, naphthyl, pyridyl, piperazinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, isoxazolinyl, 20 thiazolinyl, pyrazolinyl, morpholinyl, piperidinyl, piperazinyl, pyranyl, dioxozinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, each of the C₁-10-alkyl, C₂-10-alkenyl, C₂-10-alkynyl, C₃-10-cycloalkyl, C₄-10-cycloalkenyl, C₁-10-alkylamino-, C₁-10-dialkylamino-, C₁-10-alkoxyl, C₁-10-thioalkoxyl and ring system optionally 25 substituted independently with 1-3 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, 30 ethylamino, diethylamino, propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;

R¹⁰ is H, halo, haloalkyl, CN, NO₂, C₁-10-alkyl, C₂-10-alkenyl, C₂-10-alkynyl, C₃-10-cycloalkyl or C₄-10-cycloalkenyl,

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each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl and C₄₋₁₀-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents of R¹¹, R¹² or R¹⁶,
 5 NR¹¹R¹², NR¹²R¹², OR¹¹, SR¹¹, OR¹², SR¹², C(O)R¹¹, OC(O)R¹¹, COOR¹¹, C(O)R¹², OC(O)R¹², COOR¹², C(O)NR¹¹R¹², NR¹²C(O)R¹¹, C(O)NR¹²R¹², NR¹²C(O)R¹², NR¹²C(O)NR¹¹R¹², NR¹²C(O)NR¹²R¹², NR¹²(COOR¹¹), NR¹²(COOR¹²), OC(O)NR¹¹R¹², OC(O)NR¹²R¹², S(O)₂R¹¹, S(O)₂R¹², S(O)₂NR¹¹R¹², S(O)₂NR¹²R¹², NR¹²S(O)₂NR¹¹R¹², NR¹²S(O)₂NR¹²R¹²,
 10 NR¹²S(O)₂R¹¹, NR¹²S(O)₂R¹², NR¹²S(O)₂R¹¹ or NR¹²S(O)₂R¹²;

R¹¹ is a phenyl, naphthyl, 5,6,7,8-tetrahydronaphthyl, dihydro-indenyl, pyridyl, pyrimidinyl, triazinyl, quinolinyl, tetrahydroquinolinyl, oxo-tetrahydroquinolinyl, isoquinolinyl, oxo-tetrahydroisoquinolinyl,
 15 tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, tetrahydrofuranlyl, pyrrolyl, pyrazolyl, thieno-pyrazolyl, tetrahydropentapyrazolyl, imidazolyl, triazolyl, tetrazolyl, thiazolyl, thiadiazolyl, benzothiazolyl, oxazolyl, oxadiazolyl, benzoxazolyl,
 20 benzoxadiazolyl, isoxazolyl, isothiazolyl, indolyl, azaindolyl, 2,3-dihydroindolyl, isoindolyl, indazolyl, benzofuranlyl, benzothiophenyl, benzimidazolyl, imidazo-pyridinyl, purinyl, benzotriazolyl, oxazolinyl, isoxazolinyl, thiazolinyl, pyrrolidinyl, pyrazolinyl,
 25 morpholinyl, piperidinyl, piperazinyl, pyranlyl, dioxozinyl, 2,3-dihydro-1,4-benzoxazinyl, 1,3-benzodioxolyl, cyclopropyl, cyclobutyl, azetidyl, cyclopentyl, cyclohexyl or cycloheptyl ring system, said ring system optionally substituted independently with 1-3 substituents of R¹², R¹³,
 30 R¹⁴ or R¹⁶;

alternatively, R¹⁰ and R¹¹ taken together form a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally

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substituted independently with 1-3 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which is optionally substituted independently with 1-3 substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} , SR^{14} , OR^{15} , SR^{15} , $C(O)R^{14}$, $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$, $C(O)NR^{15}R^{15}$, $NR^{14}C(O)R^{14}$, $NR^{15}C(O)R^{14}$, $NR^{14}C(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(O)NR^{14}R^{15}$, $NR^{15}C(O)NR^{15}R^{15}$, $NR^{15}(COOR^{14})$, $NR^{15}(COOR^{15})$, $OC(O)NR^{14}R^{15}$, $OC(O)NR^{15}R^{15}$, $S(O)_2R^{14}$, $S(O)_2R^{15}$, $S(O)_2NR^{14}R^{15}$, $S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2NR^{14}R^{15}$, $NR^{15}S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2R^{14}$ or $NR^{15}S(O)_2R^{15}$;

R^{14} is phenyl, pyridyl, pyrimidinyl, thiophenyl, furyl, tetrahydrofuryl, pyrrolyl, pyrazolyl, thieno-pyrazolyl, imidazolyl, triazolyl, thiazolyl, thiadiazolyl, benzothiazolyl, oxazolyl, oxadiazolyl, benzoxazolyl, benzoxadiazolyl, isoxazolyl, isothiazolyl, indolyl, azaindolyl, isoindolyl, indazolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, pyrrolidinyl, pyrazolinyl, morpholinyl, piperidinyl, piperazinyl, 2,3-dihydro-1,4-benzoxazinyl, 1,3-benzodioxolyl, cyclopropyl, cyclobutyl, azetidiny, cyclopentyl and cyclohexyl, each of which is optionally substituted independently with 1-3 substituents of R^{15} or R^{16} ;

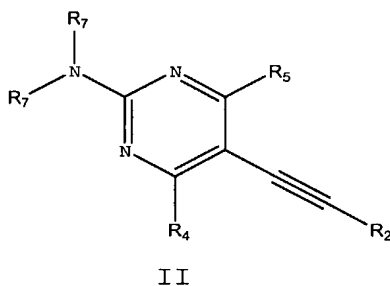
R^{15} is H or C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkoxyl, each of which is optionally substituted independently with 1-3 substituents of R^{16} ; and

R^{16} is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino,

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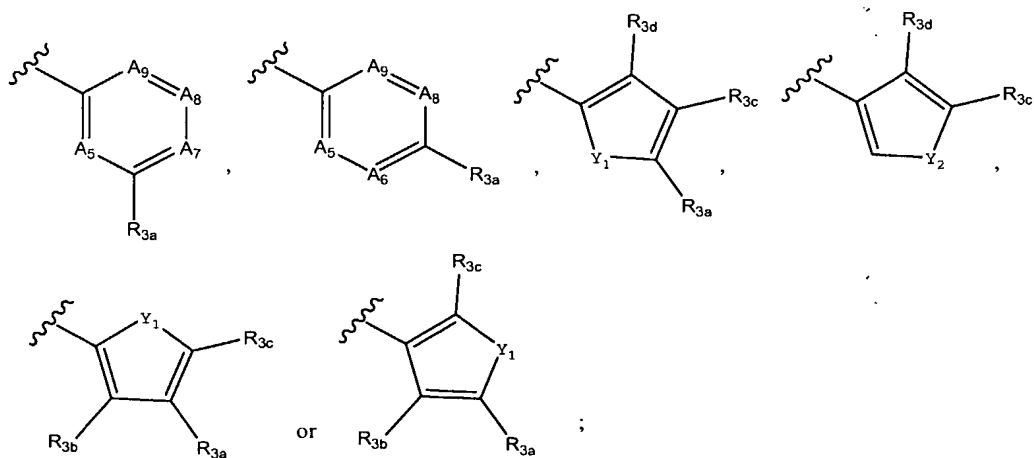
dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

13. The compound of Claim 1, having a general Formula II



wherein

R² is



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wherein

each of A⁵, A⁶, and A⁷ is, independently, CR^{3b} or N;

A⁸ is CR^{3c} or N; and

5 A⁹ is CR^{3d} or N;

Y¹ is O or S;

Y² is NR^{3a};

10 R^{3a} is COOR¹⁰, COOR¹¹, C(O)SR¹⁰, C(O)SR¹¹,
C(O)NR¹⁰R¹⁰, C(S)NR¹⁰R¹⁰, C(O)NR¹⁰R¹¹, C(S)NR¹⁰R¹¹,
NR¹⁰C(O)R¹⁰, NR¹⁰C(S)R¹⁰, NR¹⁰C(O)R¹¹, NR¹⁰C(S)R¹¹,
NR¹⁰C(S)NR¹⁰R¹⁰, NR¹⁰C(S)NR¹⁰R¹¹, S(O)₂NR¹⁰R¹⁰, S(O)₂NR¹⁰R¹¹,
NR¹⁰S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂R¹⁰ or NR¹⁰S(O)₂R¹¹;

R^{3b} is H, halo, haloalkyl, CN, NO₂, NH₂, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-cycloalkyl;

15 R^{3c} is H, halo, haloalkyl, CN, NO₂, NH₂, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-cycloalkyl;

R^{3c} is H, halo, haloalkyl, CN, NO₂, NH₂, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-cycloalkyl;

20 R^{3d} is H, halo, haloalkyl, CN, NO₂, NH₂, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-cycloalkyl;
and

alternatively, R^{3c} and R^{3d} taken together with the atoms to which they are attached form a phenyl or tetrahydrofuran ring system, optionally substituted
25 with 1-3 substituents of halo, haloalkyl, CN, NO₂, NH₂, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-cycloalkyl;

R⁴ is H, C₁₋₁₀-alkyl or O-C₁₋₁₀-alkyl;

R⁵ is H, C₁₋₁₀-alkyl or O-C₁₋₁₀-alkyl;

30 R⁷ is H or C₁₋₁₀-alkyl;

R⁸ is H or C₁₋₁₀-alkyl;

R¹⁰ is H, halo, haloalkyl, CN, NO₂, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl or C₄₋₁₀-cycloalkenyl,
each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-

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- cycloalkyl and C₄₋₁₀-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents of R¹¹, R¹² or R¹⁶, NR¹¹R¹², NR¹²R¹², OR¹¹, SR¹¹, OR¹², SR¹², C(O)R¹¹, OC(=O)R¹¹, COOR¹¹,
 5 C(O)R¹², OC(O)R¹², COOR¹², C(O)NR¹¹R¹², NR¹²C(O)R¹¹, C(O)NR¹²R¹², NR¹²C(O)R¹², NR¹²C(O)NR¹¹R¹², NR¹²C(O)NR¹²R¹², NR¹²(COOR¹¹), NR¹²(COOR¹²), OC(O)NR¹¹R¹², OC(O)NR¹²R¹², S(O)₂R¹¹, S(O)₂R¹², S(O)₂NR¹¹R¹², S(O)₂NR¹²R¹², NR¹²S(O)₂NR¹¹R¹², NR¹²S(O)₂NR¹²R¹², NR¹²S(O)₂R¹¹, NR¹²S(O)₂R¹², NR¹²S(O)₂R¹¹ or NR¹²S(O)₂R¹²;
- 10 R¹¹ is a phenyl, naphthyl, 5,6,7,8-tetrahydronaphthyl, dihydro-indenyl, pyridyl, pyrimidinyl, triazinyl, quinolinyl, tetrahydroquinolinyl, oxo-tetrahydroquinolinyl, isoquinolinyl, oxo-tetrahydroisoquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl,
 15 thiophenyl, furyl, tetrahydrofuranlyl, pyrrolyl, pyrazolyl, thieno-pyrazolyl, tetrahydropentapyrazolyl, imidazolyl, triazolyl, tetrazolyl, thiazolyl, thiadiazolyl, benzothiazolyl, oxazolyl, oxadiazolyl, benzoxazolyl, benzoxadiazolyl, isoxazolyl, isothiazolyl, indolyl,
 20 azaindolyl, 2,3-dihydroindolyl, isoindolyl, indazolyl, benzofuranlyl, benzothiophenyl, benzimidazolyl, imidazo-pyridinyl, purinyl, benzotriazolyl, oxazolinyll, isoxazolinyll, thiazolinyll, pyrrolidinyl, pyrazolinyll, morpholinyll, piperidinyl, piperazinyl, pyranlyl, dioxozinyl,
 25 2,3-dihydro-1,4-benzoxazinyl, 1,3-benzodioxolyl, cyclopropyl, cyclobutyl, azetidinyll, cyclopentyl, cyclohexyl or cycloheptyl ring system, said ring system optionally substituted independently with 1-3 substituents of R¹², R¹³, R¹⁴ or R¹⁶;
- 30 alternatively, R¹⁰ and R¹¹ taken together form a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally

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substituted independently with 1-3 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which is optionally substituted independently with 1-3 substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} , SR^{14} , OR^{15} , SR^{15} , $C(O)R^{14}$, $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$, $C(O)NR^{15}R^{15}$, $NR^{14}C(O)R^{14}$, $NR^{15}C(O)R^{14}$, $NR^{14}C(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(O)NR^{14}R^{15}$, $NR^{15}C(O)NR^{15}R^{15}$, $NR^{15}(COOR^{14})$, $NR^{15}(COOR^{15})$, $OC(O)NR^{14}R^{15}$, $OC(O)NR^{15}R^{15}$, $S(O)_2R^{14}$, $S(O)_2R^{15}$, $S(O)_2NR^{14}R^{15}$, $S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2NR^{14}R^{15}$, $NR^{15}S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2R^{14}$ or $NR^{15}S(O)_2R^{15}$;

R^{14} is phenyl, pyridyl, pyrimidinyl, thiophenyl, furyl, tetrahydrofuryl, pyrrolyl, pyrazolyl, thieno-pyrazolyl, imidazolyl, triazolyl, thiazolyl, thiadiazolyl, benzothiazolyl, oxazolyl, oxadiazolyl, benzoxazolyl, benzoxadiazolyl, isoxazolyl, isothiazolyl, indolyl, azaindolyl, isoindolyl, indazolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, pyrrolidinyl, pyrazolinyl, morpholinyl, piperidinyl, piperazinyl, 2,3-dihydro-1,4-benzoxazinyl, 1,3-benzodioxolyl, cyclopropyl, cyclobutyl, azetidyl, cyclopentyl and cyclohexyl, each of which is optionally substituted independently with 1-3 substituents of R^{15} or R^{16} ;

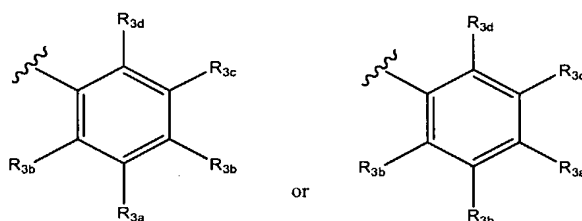
R^{15} is H or C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkoxyl, each of which is optionally substituted independently with 1-5 substituents of R^{16} ; and

R^{16} is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino,

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dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

14. The compound of claim 13 wherein
15 R² is



wherein

R^{3a} is COOR¹⁰, COOR¹¹, C(O)SR¹⁰, C(O)SR¹¹, C(O)NR¹⁰R¹⁰, C(O)NR¹⁰R¹¹, NR¹⁰C(O)R¹⁰, NR¹⁰C(O)R¹¹, S(O)₂NR¹⁰R¹⁰, S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂R¹⁰ or NR¹⁰S(O)₂R¹¹;

each of R^{3b}, R^{3c} and R^{3d}, independently, is H, F, Cl, Br, I, CF₃, CF₂CF₃, OCF₃, OCF₂CF₃, CN, NO₂, NH₂, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, acetylenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, OH, methoxyl, ethoxyl, propoxyl, SH, thiomethyl or thioethyl;

each of R⁴ and R⁵, independently, is H, F, Cl, Br, I, CF₃, CF₂CF₃, OCF₃, CN, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, OH, methoxyl, ethoxyl, propoxyl;

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- each R^7 , independently, is H, $C(O)R^8$, $COOR^8$, $C(O)R^9$, $COOR^9$, $C(O)NR^8R^9$, $C(O)NR^9R^9$, $S(O)_2R^8$, $S(O)_2NR^8R^9$, $S(O)_2R^9$, $S(O)_2NR^9R^9$, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl and C_{3-10} -cycloalkyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents of NR^8R^9 , NR^9R^9 , OR^8 , SR^8 , OR^9 , SR^9 , $C(O)R^8$, $C(O)R^9$, $C(O)NR^8R^9$, $C(O)NR^9R^9$, $NR^9C(O)R^8$, $NR^9C(O)R^9$, $NR^9C(O)NR^8R^9$, $NR^9C(O)NR^9R^9$, $NR^9(COOR^8)$, $NR^9(COOR^9)$, $S(O)_2R^8$, $S(O)_2NR^8R^9$, $S(O)_2R^9$, $S(O)_2NR^9R^9$, $NR^9S(O)_2NR^8R^9$, $NR^9S(O)_2NR^9R^9$, $NR^9S(O)_2R^8$, $NR^9S(O)_2R^9$, R^8 or R^9 ;
- R^8 is a phenyl, naphthyl, pyridyl, piperazinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuranyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl, pyrazolyl, morpholyl, piperidinyl, piperazinyl, pyranyl, dioxozinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl or cycloheptyl ring system, said ring system optionally substituted independently with 1-3 substituents of R^9 , oxo, NR^9R^9 , OR^9 , SR^9 , $C(O)R^9$, phenyl, pyridyl, piperidyl, piperazinyl or morpholyl;
- R^9 is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , acetyl, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl, C_{1-10} -thioalkoxyl or a ring system selected from phenyl, naphthyl, pyridyl, piperazinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuranyl, pyrrolidinyl, oxazolyl, isoxazolyl, thiazolyl,

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pyrazolinyl, morpholinyl, piperidinyl, piperazinyl, pyranyl and dioxozinyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl and ring system

5 optionally substituted independently with 1-3 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, propylamine, isopropylamine,

10 dipropylamine, diisopropylamine, benzyl or phenyl;

R¹⁰ is H, methyl, ethyl, propyl, isopropyl, n-butyl, sec-butyl, tert-butyl, acetylenyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl, OH, methoxyl, ethoxyl, propoxyl, SH, thiomethyl or thioethyl; each of which is optionally

15 substituted with one or more substituents of R¹¹, R¹² or R¹⁶;

R¹¹ is a phenyl, naphthyl, 5,6,7,8-tetrahydronaphthyl, dihydro-indenyl, pyridyl, pyrimidinyl, triazinyl, quinolinyl, tetrahydroquinolinyl, oxo-tetrahydroquinolinyl, isoquinolinyl, oxo-tetrahydroisoquinolinyl,

20 tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, tetrahydrofuranlyl, pyrrolyl, pyrazolyl, thieno-pyrazolyl, tetrahydropentapyrazolyl, imidazolyl, triazolyl, tetrazolyl, thiazolyl, thiadiazolyl, benzothiazolyl, oxazolyl, oxadiazolyl, benzoxazolyl,

25 benzoxadiazolyl, isoxazolyl, isothiazolyl, indolyl, azaindolyl, 2,3-dihydroindolyl, isoindolyl, indazolyl, benzofuranlyl, benzothiophenyl, benzimidazolyl, imidazo-pyridinyl, purinyl, benzotriazolyl, oxazolinyl, isoxazolinyl, thiazolinyl, pyrrolidinyl, pyrazolinyl,

30 morpholinyl, piperidinyl, piperazinyl, pyranyl, dioxozinyl, 2,3-dihydro-1,4-benzoxazinyl, 1,3-benzodioxolyl, cyclopropyl, cyclobutyl, azetidyl, cyclopentyl, cyclohexyl or cycloheptyl ring system, said ring system optionally

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substituted independently with 1-3 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

alternatively, R^{10} and R^{11} taken together form a partially or fully saturated or unsaturated 5-6 membered
5 ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-3 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -
10 cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which is optionally substituted independently with 1-3 substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} , SR^{14} , OR^{15} , SR^{15} , $C(O)R^{14}$,
15 $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$,
 $C(O)NR^{15}R^{15}$, $NR^{14}C(O)R^{14}$, $NR^{15}C(O)R^{14}$, $NR^{14}C(O)R^{15}$, $NR^{15}C(O)R^{15}$,
 $NR^{15}C(O)NR^{14}R^{15}$, $NR^{15}C(O)NR^{15}R^{15}$, $NR^{15}(COOR^{14})$, $NR^{15}(COOR^{15})$,
 $OC(O)NR^{14}R^{15}$, $OC(O)NR^{15}R^{15}$, $S(O)_2R^{14}$, $S(O)_2R^{15}$, $S(O)_2NR^{14}R^{15}$,
 $S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2NR^{14}R^{15}$, $NR^{15}S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2R^{14}$ or
20 $NR^{15}S(O)_2R^{15}$;

R^{14} is phenyl, pyridyl, pyrimidinyl, thiophenyl, furyl, tetrahydrofuryl, pyrrolyl, pyrazolyl, thieno-pyrazolyl, imidazolyl, triazolyl, thiazolyl, thiadiazolyl, benzothiazolyl, oxazolyl, oxadiazolyl, benzoxazolyl,
25 benzoxadiazolyl, isoxazolyl, isothiazolyl, indolyl, azaindolyl, isoindolyl, indazolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, pyrrolidinyl, pyrazolinyl, morpholinyl, piperidinyl, piperazinyl, 2,3-dihydro-1,4-benzoxazinyl, 1,3-benzodioxolyl, cyclopropyl, cyclobutyl,
30 azetidiny, cyclopentyl and cyclohexyl, each of which is optionally substituted independently with 1-3 substituents of R^{15} or R^{16} ;

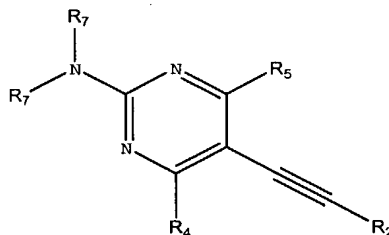
R^{15} is H or C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -

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dialkylamino-, C₁₋₁₀-alkoxyl or C₁₋₁₀-thioalkoxyl, each of which is optionally substituted independently with 1-3 substituents of R¹⁶; and

R¹⁶ is H, halo, haloalkyl, CN, OH, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

15. The compound of Claim 8, having a general Formula II



wherein

R² is a phenyl, naphthyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl or isoindolyl ring system, said ring system substituted independently with 0-3 substituents of R¹⁰, R¹¹ or R¹⁵ and one substituent, meta or para to the point of attachment of the alkyne on the R²

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ring, is $\text{NR}^{10}\text{C}(\text{O})\text{NR}^{10}\text{R}^{10}$, $\text{NR}^{10}\text{C}(\text{O})\text{NR}^{10}\text{R}^{11}$, $\text{NR}^{10}(\text{COOR}^{10})$ or $\text{NR}^{10}(\text{COOR}^{11})$;

R^7 is H, C_{1-10} -alkyl or C_{3-10} -cycloalkyl, each of the C_{1-10} -alkyl and C_{3-10} -cycloalkyl optionally comprising 1-2
5 heteroatoms selected from N, O and S and optionally substituted with 1-3 substituents of R^9 ;

R^8 is a phenyl, naphthyl, pyridyl, pyrimidinyl, pyrrolidinyl, piperidinyl, piperazinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl,
10 tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, tetrahydroquinazolinyl, tetrahydroisoquinazolinyl, morpholinyl, thiophenyl, furyl, dihydrofuryl, tetrahydrofuryl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl,
15 benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl ring system, said ring system optionally substituted independently with 1-3 substituents of R^9 , oxo, NR^9R^9 , OR^9 , SR^9 , $\text{C}(\text{O})\text{R}^9$ or a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally
20 including 1-3 heteroatoms selected from O, N, or S, and optionally substituted independently with 1-3 substituents of R^9 ;

alternatively, R^7 and R^8 taken together form a 5-6 membered ring selected from pyrrolidine, piperidine,
25 morpholine and piperazine, the ring optionally substituted independently with 1-3 substituents of R^9 ;

R^9 is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , acetyl, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl, C_{1-10} -thioalkoxyl or a ring system of phenyl, naphthyl, pyridyl,
30 pyrimidinyl, pyrrolidinyl, piperidinyl, piperazinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, tetrahydroquinazolinyl, tetrahydroisoquinazolinyl,

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- morpholinyl, thiophenyl, furyl, dihydrofuryl, tetrahydrofuryl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl and
- 5 benzimidazolyl, wherein each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl and ring system is optionally substituted independently with 1-3 substituents of halo, haloalkyl, CN,
- 10 NO₂, NH₂, OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamine, dimethylamine, ethylamine, diethylamine, propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;
- 15 R¹⁰ is H, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl or C₃₋₁₀-cycloalkyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl and C₃₋₁₀-cycloalkyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-3 substituents of R¹¹, R¹² or R¹⁶, NR¹¹R¹²,
- 20 NR¹²R¹², OR¹¹, SR¹¹, OR¹², SR¹², C(O)R¹¹, OC(O)R¹¹, COOR¹¹, C(O)R¹², OC(O)R¹², COOR¹², C(O)NR¹¹R¹², NR¹²C(O)R¹¹, C(O)NR¹²R¹², NR¹²C(O)R¹², NR¹²C(O)NR¹¹R¹², NR¹²C(O)NR¹²R¹², NR¹²(COOR¹¹), NR¹²(COOR¹²), OC(O)NR¹¹R¹², OC(O)NR¹²R¹², S(O)₂R¹¹, S(O)₂R¹², S(O)₂NR¹¹R¹², S(O)₂NR¹²R¹², NR¹²S(O)₂NR¹¹R¹², NR¹²S(O)₂NR¹²R¹²,
- 25 NR¹²S(O)₂R¹¹, NR¹²S(O)₂R¹², NR¹²S(O)₂R¹¹ or NR¹²S(O)₂R¹²;
- R¹¹ is a phenyl, naphthyl, pyridyl, pyrimidinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, tetrahydroquinazolinyl, tetrahydroisoquinazolinyl,
- 30 thiophenyl, furyl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl, benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl ring system, said ring

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system optionally substituted independently with 1-3 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

alternatively, R^{10} and R^{11} taken together form a partially or fully saturated or unsaturated 5-6 membered
5 ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, said ring optionally substituted independently with 1-3 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which
10 is optionally substituted independently with 1-3 substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} , SR^{14} , OR^{15} , SR^{15} , $C(O)R^{14}$, $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$,
15 $C(O)NR^{15}R^{15}$, $NR^{14}C(O)R^{14}$, $NR^{15}C(O)R^{14}$, $NR^{14}C(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(O)NR^{14}R^{15}$, $NR^{15}C(O)NR^{15}R^{15}$, $NR^{15}(COOR^{14})$, $NR^{15}(COOR^{15})$, $OC(O)NR^{14}R^{15}$, $OC(O)NR^{15}R^{15}$, $S(O)_2R^{14}$, $S(O)_2R^{15}$, $S(O)_2NR^{14}R^{15}$, $S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2NR^{14}R^{15}$, $NR^{15}S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2R^{14}$ or $NR^{15}S(O)_2R^{15}$;

R^{14} is phenyl, naphthyl, pyridyl, pyrimidinyl, pyrrolidinyl, piperidinyl, piperazinyl, quinolinyl, isoquinolinyl, tetrahydroquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, tetrahydroquinazolinyl, tetrahydroisoquinazolinyl,
25 morpholinyl, thiophenyl, furyl, dihydrofuryl, tetrahydrofuryl, pyrrolyl, imidazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, indolinyl, benzofuranyl, dihydrobenzofuranyl, benzoxazinyl, benzodioxazinyl, benzothiophenyl and benzimidazolyl, each of
30 which is optionally substituted independently with 1-5 substituents of R^{15} or R^{16} ;

R^{15} is H or C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkoxyl, each of

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which is optionally substituted independently with 1-5 substituents of R^{16} ; and

R^{16} is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO_2 , NH_2 , OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

16. The compound of Claim 1, wherein

A^1 and A^4 , independently, are N;

A^2 is CR^4 ;

A^3 is CR^5 ;

R^1 is SR^7 , OR^8 , SR^8 , $C(O)R^7$, $OC(O)R^7$, $COOR^7$, $C(O)R^8$, $OC(O)R^8$, $COOR^8$, $C(O)NR^7R^7$, $C(S)NR^7R^7$, $NR^7C(O)R^7$, $NR^7C(S)R^7$, $NR^7C(O)NR^7R^7$, $NR^7C(S)NR^7R^7$, $NR^7(COOR^7)$, $OC(O)NR^7R^7$, $C(O)NR^7R^8$, $C(S)NR^7R^8$, $NR^7C(O)R^8$, $NR^7C(S)R^8$, $NR^7C(O)NR^7R^8$, $NR^7C(S)NR^7R^8$, $NR^7(COOR^8)$, $OC(O)NR^7R^8$, $S(O)_2R^7$, $S(O)_2NR^7R^7$, $NR^7S(O)_2NR^7R^7$, $NR^7S(O)_2R^7$, $S(O)_2R^8$, $S(O)_2NR^7R^8$, $NR^7S(O)_2NR^7R^8$ or $NR^7S(O)_2R^8$;

R^2 is a phenyl, naphthyl, pyridyl, pyrimidinyl, pyridazinyl, pyrazinyl, triazinyl, quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, phthalazinyl, aza-phthalazinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, pyrazolyl, triazolyl, thiazolyl, thiadiazolyl, oxazolyl, isoxazolyl, oxadiazolyl, isothiazolyl, indolyl, isoindolyl,

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benzofuranyl, dihydrobenzofuranyl, benzothiophenyl or benzimidazolyl ring system, said ring system substituted independently with 1-5 substituents of R^{10} , R^{11} , R^{15} , $NR^{10}R^{10}$, $NR^{10}R^{11}$, OR^{10} , SR^{10} , OR^{11} , SR^{11} , $C(O)R^{10}$, $C(S)R^{10}$, $C(NCN)R^{10}$,
 5 $C(O)R^{11}$, $C(S)R^{11}$, $C(NCN)R^{11}$, $C(O)C(O)R^{10}$, $OC(O)R^{10}$, $COOR^{10}$, $C(O)SR^{10}$, $C(O)C(O)R^{11}$, $OC(O)R^{11}$, $COOR^{11}$, $C(O)SR^{11}$, $C(O)NR^{10}R^{10}$, $C(S)NR^{10}R^{10}$, $C(O)NR^{10}R^{11}$, $C(S)NR^{10}R^{11}$, $OC(O)NR^{10}R^{11}$, $NR^{10}C(O)R^{10}$, $NR^{10}C(O)R^{11}$, $NR^{10}C(S)R^{10}$, $NR^{10}C(S)R^{11}$, $NR^{10}C(O)NR^{10}R^{10}$, $NR^{10}C(O)NR^{10}R^{11}$, $NR^{10}C(S)NR^{10}R^{10}$, $NR^{10}C(S)NR^{10}R^{11}$, $NR^{10}(COOR^{10})$,
 10 $NR^{10}(COOR^{11})$, $NR^{10}C(O)C(O)R^{10}$, $NR^{10}C(O)C(O)R^{11}$, $NR^{10}C(O)C(O)NR^{10}R^{11}$, $S(O)_2R^{10}$, $S(O)_2R^{11}$, $S(O)_2NR^{10}R^{10}$, $S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2R^{10}$ or $NR^{10}S(O)_2R^{11}$, provided that (1) one substituent is $C(O)R^{10}$, $COOR^{10}$, $C(O)R^{11}$, $COOR^{11}$, $C(O)NR^{10}R^{10}$, $C(S)NR^{10}R^{10}$, $C(O)NR^{10}R^{11}$, $C(S)NR^{10}R^{11}$, $NR^{10}C(O)R^{10}$,
 15 $NR^{10}C(S)R^{10}$, $NR^{10}C(O)R^{11}$, $NR^{10}C(S)R^{11}$, $NR^{10}C(O)NR^{10}R^{10}$, $NR^{10}C(O)NR^{10}R^{11}$, $NR^{10}(COOR^{10})$, $NR^{10}(COOR^{11})$, $NR^{10}C(S)NR^{10}R^{10}$, $NR^{10}C(S)NR^{10}R^{11}$, $S(O)_2NR^{10}R^{10}$, $S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2NR^{10}R^{11}$, $NR^{10}S(O)_2R^{10}$ or $NR^{10}S(O)_2R^{11}$;

R^4 is H, halo, haloalkyl, NO_2 , CN, NR^7R^7 , OR^7 , SR^7 ,
 20 $C(O)R^7$, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl and C_{3-10} -cycloalkyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-3 substituents of R^9 ;

25 R^5 is H, halo, haloalkyl, NO_2 , CN, NR^7R^7 , OR^7 ; SR^7 , $C(O)R^7$, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl and C_{3-10} -cycloalkyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally
 30 substituted with 1-3 substituents of R^9 ;

R^7 is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl or C_{4-10} -cycloalkenyl, each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl and C_{4-10} -cycloalkenyl optionally comprising 1-4 heteroatoms selected

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from N, O and S and optionally substituted with 1-3 substituents of NR^8R^9 , NR^9R^9 , OR^8 , SR^8 , OR^9 , SR^9 , $\text{C}(\text{O})\text{R}^8$, $\text{OC}(\text{O})\text{R}^8$, COOR^8 , $\text{C}(\text{O})\text{R}^9$, $\text{OC}(\text{O})\text{R}^9$, COOR^9 , $\text{C}(\text{O})\text{NR}^8\text{R}^9$, $\text{C}(\text{O})\text{NR}^9\text{R}^9$, $\text{NR}^9\text{C}(\text{O})\text{R}^8$, $\text{NR}^9\text{C}(\text{O})\text{R}^9$, $\text{NR}^9\text{C}(\text{O})\text{NR}^8\text{R}^9$, $\text{NR}^9\text{C}(\text{O})\text{NR}^9\text{R}^9$, $\text{NR}^9(\text{COOR}^8)$, $\text{NR}^9(\text{COOR}^9)$, $\text{OC}(\text{O})\text{NR}^8\text{R}^9$, $\text{OC}(\text{O})\text{NR}^9\text{R}^9$, $\text{S}(\text{O})_2\text{R}^8$, $\text{S}(\text{O})_2\text{NR}^8\text{R}^9$, $\text{S}(\text{O})_2\text{R}^9$, $\text{S}(\text{O})_2\text{NR}^9\text{R}^9$, $\text{NR}^9\text{S}(\text{O})_2\text{NR}^8\text{R}^9$, $\text{NR}^9\text{S}(\text{O})_2\text{NR}^9\text{R}^9$, $\text{NR}^9\text{S}(\text{O})_2\text{R}^8$, $\text{NR}^9\text{S}(\text{O})_2\text{R}^9$, R^8 or R^9 ;

R^8 is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein said ring system is optionally substituted independently with 1-5 substituents of R^9 , oxo, NR^9R^9 , OR^9 , SR^9 , $\text{C}(\text{O})\text{R}^9$ or a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and optionally substituted independently with 1-3 substituents of R^9 ;

alternatively, R^7 and R^8 taken together form a saturated or partially or fully unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally substituted independently with 1-3 substituents of R^9 ;

R^9 is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , acetyl, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl, C_{1-10} -thioalkoxyl or a saturated or partially or fully unsaturated 5-8 membered monocyclic or a 6-12 membered bicyclic, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, wherein each of the C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -

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dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl and ring of said ring system is optionally substituted independently with 1-3 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamine, dimethylamine, ethylamine, diethylamine, propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;

R¹⁰ is H, halo, haloalkyl, CN, NO₂, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl or C₄₋₁₀-cycloalkenyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl and C₄₋₁₀-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with 1-5 substituents of R¹¹, R¹² or R¹⁶, NR¹¹R¹², NR¹²R¹², OR¹¹, SR¹¹, OR¹², SR¹², C(O)R¹¹, OC(O)R¹¹, COOR¹¹, C(O)R¹², OC(O)R¹², COOR¹², C(O)NR¹¹R¹², NR¹²C(O)R¹¹, C(O)NR¹²R¹², NR¹²C(O)R¹², NR¹²C(O)NR¹¹R¹², NR¹²C(O)NR¹²R¹², NR¹²(COOR¹¹), NR¹²(COOR¹²), OC(O)NR¹¹R¹², OC(O)NR¹²R¹², S(O)₂R¹¹, S(O)₂R¹², S(O)₂NR¹¹R¹², S(O)₂NR¹²R¹², NR¹²S(O)₂NR¹¹R¹², NR¹²S(O)₂NR¹²R¹², NR¹²S(O)₂R¹¹, NR¹²S(O)₂R¹², NR¹²S(O)₂R¹¹ or NR¹²S(O)₂R¹²;

R¹¹ is a partially or fully saturated or unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein each ring of said ring system is optionally substituted independently with 1-5 substituents of R¹², R¹³, R¹⁴ or R¹⁶;

alternatively, R¹⁰ and R¹¹ taken together form a partially or fully saturated or unsaturated 5-6 membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, and the ring optionally

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substituted independently with 1-5 substituents of R^{12} , R^{13} , R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which is optionally substituted independently with 1-5 substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} , SR^{14} , OR^{15} , SR^{15} , $C(O)R^{14}$, $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$, $C(O)NR^{15}R^{15}$, $NR^{14}C(O)R^{14}$, $NR^{15}C(O)R^{14}$, $NR^{14}C(O)R^{15}$, $NR^{15}C(O)R^{15}$, $NR^{15}C(O)NR^{14}R^{15}$, $NR^{15}C(O)NR^{15}R^{15}$, $NR^{15}(COOR^{14})$, $NR^{15}(COOR^{15})$, $OC(O)NR^{14}R^{15}$, $OC(O)NR^{15}R^{15}$, $S(O)_2R^{14}$, $S(O)_2R^{15}$, $S(O)_2NR^{14}R^{15}$, $S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2NR^{14}R^{15}$, $NR^{15}S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2R^{14}$ or $NR^{15}S(O)_2R^{15}$;

R^{14} is a partially or fully saturated or unsaturated 5-8 membered or a saturated or partially or fully unsaturated 5-8 membered monocyclic, 6-12 membered bicyclic, or 7-14 membered tricyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic, 1-6 heteroatoms if bicyclic, or 1-9 heteroatoms if tricyclic, said heteroatoms selected from O, N, or S, and wherein each ring of said ring system is optionally substituted independently with 1-5 substituents of R^{15} or R^{16} ;

R^{15} is H or C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkoxyl, each of which is optionally substituted independently with 1-5 substituents of R^{16} ;

R^{16} is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a

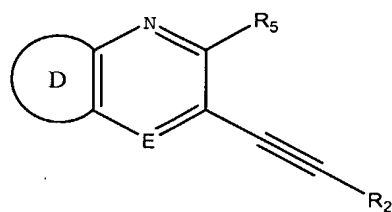
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partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl; and provided that (1) when said at least one substituent on said R² ring system is C(O)NR¹⁰R¹⁰ or C(O)NR¹⁰R¹¹, then R¹⁰ and R¹¹, independently, are not -CH₂-L-Q or -C(C₁₋₆alkyl)(C₁₋₆alkyl)-L-Q, wherein L is -O-, -NH-, -NHC(O)-, -NHC(O)N-, -NHC(=NH)N- or -CO₂- and Q is H, substituted or unsubstituted C₁₋₆alkyl, substituted or unsubstituted aryl, substituted or unsubstituted heterocyclyl, substituted or unsubstituted heteraryl or C₁₋₆alkyl substituted with aryl, heterocyclyl or heteroaryl; or (2) when said R² is a phenyl ring substituted with C(O)NR¹⁰R¹⁰ or C(O)NR¹⁰R¹¹ meta to the point of attachment of the alkynyl group on R² of Formula I, then either (a) R¹ is not halogen, C₁₋₆alkyl, C₁₋₆alkoxyl or hydroxyl or (b) where R¹ and R³ taken together with the atoms to which they are attached form a partially or fully unsaturated 5- or 6-membered ring of carbon atoms optionally including 1-3 heteroatoms selected from O, N, or S, said ring is not substituted with halogen, C₁₋₆alkyl, C₁₋₆alkoxyl or hydroxyl substituents.

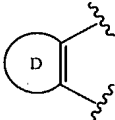
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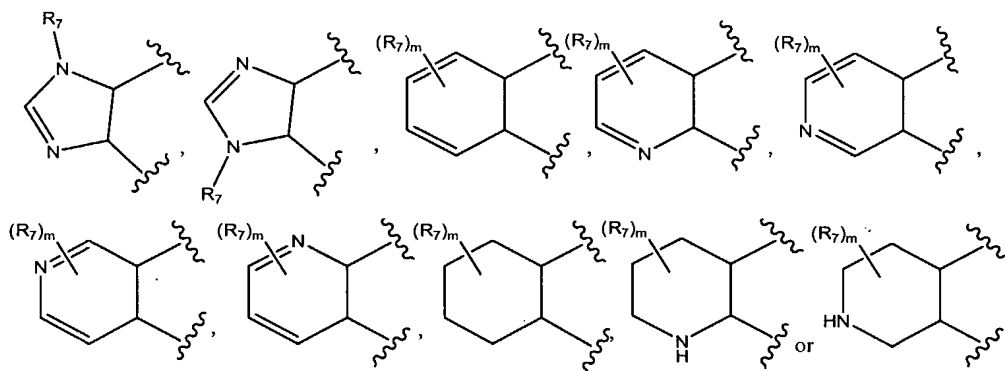
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17. A compound having a general Formula III



III

wherein  is

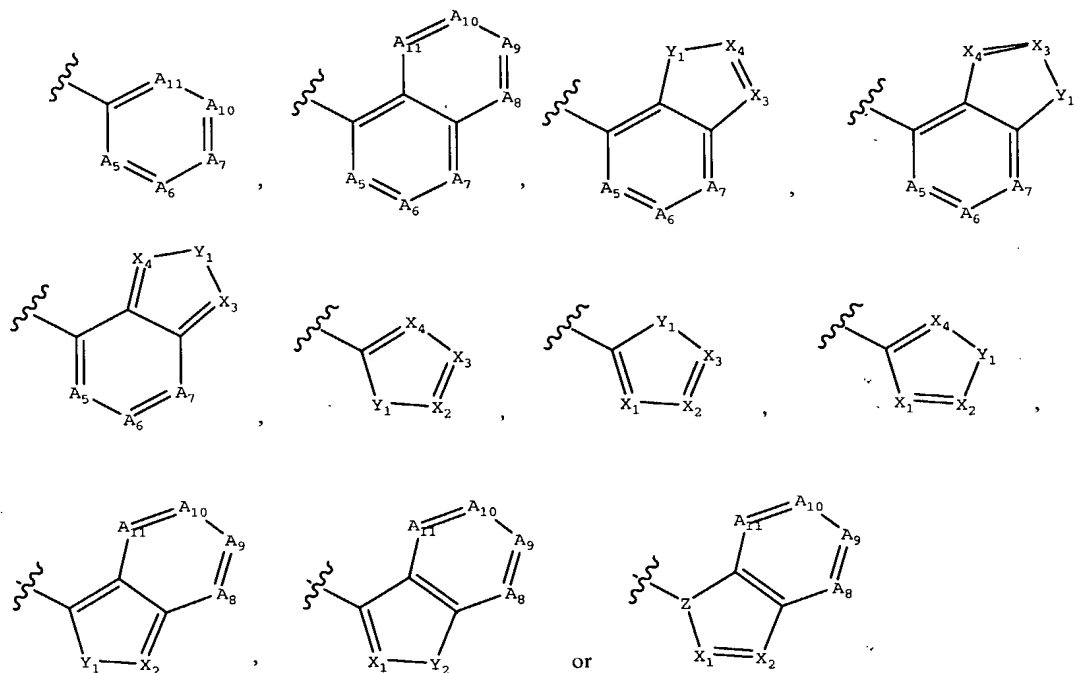


5

wherein m is 0, 1, 2 or 3;

E is CR⁴ or N;R² is

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wherein

one of A⁶ and A⁷ is CR^{3a} and the other of A⁶ and A⁷ is CR^{3b} or N;

5 each of A⁵, A⁸, A⁹, A¹⁰ and A¹¹ is, independently, CR^{3b} or N;

X² is CR^{3a};

each of X¹, X³ and X⁴ is, independently, CR^{3b} or N;

Y¹ is CR^{3b}R^{3c}, NR^{3c}, O or S;

10 Y² is CR^{3a}R^{3b} or NR^{3a}; and

Z is CH or N;

R^{3a} is C(O)OC₁₋₃-alkylR¹¹, OC(O)R¹¹, COOR¹¹, C(O)SC₁₋₃-alkylR¹¹, C(O)SR¹¹, C(O)N(R¹⁰)C₁₋₃-alkylR¹¹, C(S)N(R¹⁰)C₁₋₃-alkylR¹¹, C(O)NR¹⁰R¹¹, C(S)NR¹⁰R¹¹, NR¹⁰C(O)C₁₋₃-alkylR¹¹,
 15 NR¹⁰C(S)C₁₋₃-alkylR¹¹, NR¹⁰C(O)R¹¹, NR¹⁰C(S)R¹¹,
 NR¹⁰C(O)N(R¹⁰)C₁₋₃-alkylR¹¹, NR¹⁰C(O)NR¹⁰R¹¹, NR¹⁰C(S)N(R¹⁰)C₁₋₃-alkylR¹¹, NR¹⁰C(S)NR¹⁰R¹¹, NR¹⁰C(O)OC₁₋₃-alkylR¹¹,
 NR¹⁰(COOR¹¹), OC(O)NR¹⁰R¹¹, S(O)₂N(R¹⁰)C₁₋₃-alkylR¹¹,
 S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂NR¹⁰R¹¹, NR¹⁰S(O)₂C₁₋₃-alkylR¹¹ or
 20 NR¹⁰S(O)₂R¹¹;

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R^{3b} is H, halo, haloalkyl, CN, NO_2 , NH_2 , C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl; and

R^{3c} is H, CN or C_{1-10} -alkyl;

5 R^4 is H, halo, haloalkyl, NO_2 , CN, OH, O- C_{1-10} -alkyl, NH_2 , C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl;

R^5 is H, halo, haloalkyl, NO_2 , CN, OH, NH_2 , O- C_{1-10} -alkyl, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl or C_{3-10} -cycloalkyl;

10 Each R^7 , independently, is H, R^8 , C_{1-10} -alkyl, C_{2-10} -alkenyl or C_{2-10} -alkynyl, each of which is optionally substituted with 1-3 substituents of NR^8R^9 , NR^9R^9 , OR^8 , SR^8 , OR^9 , SR^9 , $C(O)R^8$, $C(O)R^9$, $C(O)NR^8R^9$, $C(O)NR^9R^9$, $S(O)_2R^8$,
15 $S(O)_2NR^8R^9$, $S(O)_2R^9$, $S(O)_2NR^9R^9$, R^8 or R^9 ;

R^8 is a ring system selected from phenyl, pyridyl, piperazinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, pyrrolidinyl, oxazolinyl, isoxazolinyl, thiazolinyl,
20 pyrazolinyl, morpholinyl, piperidinyl, pyranyl, dioxozinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, said ring system optionally substituted independently with 1-3 substituents of R^9 , oxo, NR^9R^9 , OR^9 , SR^9 or $C(O)R^9$;

25 R^9 is H, halo, haloalkyl, CN, OH, NO_2 , NH_2 , acetyl, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -dialkylamino-, C_{1-10} -alkoxyl, C_{1-10} -thioalkoxyl or a ring system selected from phenyl, naphthyl, pyridyl, piperazinyl, triazinyl,
30 quinolinyl, isoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, pyrrolyl, imidazolyl, triazolyl, thiazolyl, oxazolyl, isoxazolyl, isothiazolyl, indolyl, isoindolyl, benzofuranyl, benzothiophenyl, benzimidazolyl, tetrahydrofuranyl, pyrrolidinyl, oxazolinyl, isoxazolinyl,

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- thiazolinyl, pyrazolinyl, morpholinyl, piperidinyl, piperazinyl, pyranyl, dioxozinyl, cyclopropyl, cyclobutyl, cyclopentyl, cyclohexyl and cycloheptyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl, C₁₋₁₀-thioalkoxyl and ring system optionally substituted independently with 1-3 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, oxo, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, propylamine, isopropylamine, dipropylamine, diisopropylamine, benzyl or phenyl;
- R¹⁰ is H, CN, NO₂, C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl or C₄₋₁₀-cycloalkenyl, each of the C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl and C₄₋₁₀-cycloalkenyl optionally comprising 1-4 heteroatoms selected from N, O and S and optionally substituted with one or more substituents of R¹¹, R¹² or R¹⁶, NR¹¹R¹², NR¹²R¹², OR¹¹, SR¹¹, OR¹², SR¹², C(O)R¹¹, OC(O)R¹¹, COOR¹¹, C(O)R¹², OC(O)R¹², COOR¹², C(O)NR¹¹R¹², NR¹²C(O)R¹¹, C(O)NR¹²R¹², NR¹²C(O)R¹², NR¹²C(O)NR¹¹R¹², NR¹²C(O)NR¹²R¹², NR¹²(COOR¹¹), NR¹²(COOR¹²), OC(O)NR¹¹R¹², OC(O)NR¹²R¹², S(O)₂R¹¹, S(O)₂R¹², S(O)₂NR¹¹R¹², S(O)₂NR¹²R¹², NR¹²S(O)₂NR¹¹R¹², NR¹²S(O)₂NR¹²R¹², NR¹²S(O)₂R¹¹, NR¹²S(O)₂R¹², NR¹²S(O)₂R¹¹ or NR¹²S(O)₂R¹²;
- R¹¹ is a phenyl, naphthyl, 5,6,7,8-tetrahydronaphthyl, dihydro-indenyl, pyridyl, pyrimidinyl, triazinyl, quinolinyl, tetrahydroquinolinyl, oxo-tetrahydroquinolinyl, isoquinolinyl, oxo-tetrahydroisoquinolinyl, tetrahydroisoquinolinyl, quinazolinyl, isoquinazolinyl, thiophenyl, furyl, tetrahydrofuranlyl, pyrrolyl, pyrazolyl, thieno-pyrazolyl, tetrahydropentapyrazolyl, imidazolyl, triazolyl, tetrazolyl, thiazolyl, thiadiazolyl, benzothiazolyl, oxazolyl, oxadiazolyl, benzoxazolyl, benzoxadiazolyl, isoxazolyl, isothiazolyl, indolyl,

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azaindolyl, 2,3-dihydroindolyl, isoindolyl, indazolyl,
 benzofuranyl, benzothiophenyl, benzimidazolyl, imidazo-
 pyridinyl, purinyl, benzotriazolyl, oxazoliny, 5
 isoxazoliny, thiazoliny, pyrrolidinyl, pyrazoliny,
 morpholiny, piperidinyl, piperazinyl, pyranyl, dioxoziny, 10
 2,3-dihydro-1,4-benzoxazinyl, 1,3-benzodioxolyl,
 cyclopropyl, cyclobutyl, azetidiny, cyclopentyl, cyclohexyl
 or cycloheptyl ring system, said ring system optionally
 substituted independently with 1-3 substituents of R^{12} , R^{13} ,
 10 R^{14} or R^{16} ;

alternatively, R^{10} and R^{11} taken together form a
 partially or fully saturated or unsaturated 5-6 membered
 ring of carbon atoms optionally including 1-3 heteroatoms
 selected from O, N, or S, and the ring optionally
 15 substituted independently with 1-3 substituents of R^{12} , R^{13} ,
 R^{14} or R^{16} ;

R^{12} is H, C_{1-10} -alkyl, C_{2-10} -alkenyl, C_{2-10} -alkynyl, C_{3-10} -
 cycloalkyl, C_{4-10} -cycloalkenyl, C_{1-10} -alkylamino-, C_{1-10} -
 dialkylamino-, C_{1-10} -alkoxyl or C_{1-10} -thioalkyl, each of which
 20 is optionally substituted independently with 1-3
 substituents of R^{13} , R^{14} , R^{15} or R^{16} ;

R^{13} is $NR^{14}R^{15}$, $NR^{15}R^{15}$, OR^{14} , SR^{14} , OR^{15} , SR^{15} , $C(O)R^{14}$,
 $OC(O)R^{14}$, $COOR^{14}$, $C(O)R^{15}$, $OC(O)R^{15}$, $COOR^{15}$, $C(O)NR^{14}R^{15}$,
 $C(O)NR^{15}R^{15}$, $NR^{14}C(O)R^{14}$, $NR^{15}C(O)R^{14}$, $NR^{14}C(O)R^{15}$, $NR^{15}C(O)R^{15}$,
 25 $NR^{15}C(O)NR^{14}R^{15}$, $NR^{15}C(O)NR^{15}R^{15}$, $NR^{15}(COOR^{14})$, $NR^{15}(COOR^{15})$,
 $OC(O)NR^{14}R^{15}$, $OC(O)NR^{15}R^{15}$, $S(O)_2R^{14}$, $S(O)_2R^{15}$, $S(O)_2NR^{14}R^{15}$,
 $S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2NR^{14}R^{15}$, $NR^{15}S(O)_2NR^{15}R^{15}$, $NR^{14}S(O)_2R^{14}$ or
 $NR^{15}S(O)_2R^{15}$;

R^{14} is phenyl, pyridyl, pyrimidinyl, thiophenyl, furyl,
 30 tetrahydrofuryl, pyrrolyl, pyrazolyl, thieno-pyrazolyl,
 imidazolyl, triazolyl, thiazolyl, thiadiazolyl,
 benzothiazolyl, oxazolyl, oxadiazolyl, benzoxazolyl,
 benzoxadiazolyl, isoxazolyl, isothiazolyl, indolyl,
 azaindolyl, isoindolyl, indazolyl, benzofuranyl,

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benzothiophenyl, benzimidazolyl, pyrrolidinyl, pyrazolinyl, morpholinyl, piperidinyl, piperazinyl, 2,3-dihydro-1,4-benzoxazinyl, 1,3-benzodioxolyl, cyclopropyl, cyclobutyl, azetidiny, cyclopentyl and cyclohexyl, each of which is
5 optionally substituted independently with 1-3 substituents of R¹⁵ or R¹⁶;

R¹⁵ is H or C₁₋₁₀-alkyl, C₂₋₁₀-alkenyl, C₂₋₁₀-alkynyl, C₃₋₁₀-cycloalkyl, C₄₋₁₀-cycloalkenyl, C₁₋₁₀-alkylamino-, C₁₋₁₀-dialkylamino-, C₁₋₁₀-alkoxyl or C₁₋₁₀-thioalkoxyl, each of
10 which is optionally substituted independently with 1-3 substituents of R¹⁶; and

R¹⁶ is H, halo, haloalkyl, CN, OH, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl, isobutyl, tert-butyl, methylamino,
15 dimethylamino, ethylamino, diethylamino, isopropylamino, oxo, acetyl, benzyl, phenyl, cyclopropyl, cyclobutyl or a partially or fully saturated or unsaturated 5-8 membered monocyclic or 6-12 membered bicyclic ring system, said ring system formed of carbon atoms optionally including 1-3
20 heteroatoms if monocyclic or 1-6 heteroatoms if bicyclic, said heteroatoms selected from O, N, or S, and optionally substituted independently with 1-5 substituents of halo, haloalkyl, CN, NO₂, NH₂, OH, methyl, methoxyl, ethyl, ethoxyl, propyl, propoxyl, isopropyl, cyclopropyl, butyl,
25 isobutyl, tert-butyl, methylamino, dimethylamino, ethylamino, diethylamino, isopropylamino, benzyl or phenyl.

18. The compound of Claim 1, and pharmaceutically acceptable salts thereof, selected from:
30 3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-(trifluoromethyl)phenyl)benzamide;
6-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-(trifluoromethyl)phenyl)-2-pyridinecarboxamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-

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- (trifluoromethyl)phenyl)-3-pyridinecarboxamide;
2-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-(trifluoromethyl)phenyl)-4-pyridinecarboxamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(3-(trifluoromethyl)phenyl)benzamide;
5 (trifluoromethyl)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(2-(4-methyl-1-piperazinyl)-5-(trifluoromethyl)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3-(dimethylamino)propyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-4-methylbenzamide;
10 (trifluoromethyl)phenyl)-4-methylbenzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-(dimethylamino)-5-(trifluoromethyl)phenyl)-4-methylbenzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3R)-3-(dimethylamino)-1-pyrrolidinyl)-5-(trifluoromethyl)phenyl)-4-methylbenzamide;
15 4-methylbenzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(2-(methyl(1-methyl-4-piperidinyl)amino)-5-(trifluoromethyl)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(2-(methyl((3R)-1-methyl-3-pyrrolidinyl)amino)-5-(trifluoromethyl)phenyl)benzamide;
20 (trifluoromethyl)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-(2-(dimethylamino)-1,1-dimethylethyl)-5-(trifluoromethyl)phenyl)-4-methylbenzamide;
25 3-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3S)-3-(dimethylamino)-1-piperidinyl)-5-(trifluoromethyl)phenyl)-4-methylbenzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(methyl((3S)-1-methyl-3-pyrrolidinyl)amino)-5-(trifluoromethyl)phenyl)benzamide;
30 (trifluoromethyl)phenyl)benzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(methyl((3R)-1-methyl-3-pyrrolidinyl)amino)-5-(trifluoromethyl)phenyl)benzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3-

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- (dimethylamino)propyl)(methylamino)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3R)-3-(dimethylamino)-1-pyrrolidinyl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(5-cyclohexyl-2-(methoxy)phenyl)-4-methylbenzamide;
5-((2-methyl-5-((6-(trifluoromethyl)-2,3-dihydro-1H-indol-1-yl)carbonyl)phenyl)ethynyl)-2-pyrimidinamine;
10 5-((2-methyl-5-((7-(trifluoromethyl)-3,4-dihydro-1(2H)-quinolinyl)carbonyl)phenyl)ethynyl)-2-pyrimidinamine;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-(4-(hydroxymethyl)-1H-imidazol-1-yl)-5-(trifluoromethyl)phenyl)-4-methylbenzamide;
15 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3-(dimethylamino)propyl)(methylamino)-5-(trifluoromethyl)-3-pyridinyl)-2-fluorobenzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3-(dimethylamino)propyl)(methylamino)-5-(trifluoromethyl)-3-pyridinyl)-4-methylbenzamide;
20 3-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-(trifluoromethyl)phenyl)-1H-indole-1-carboxamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-(1,2,3,6-tetrahydro-4-pyridinyl)-5-(trifluoromethyl)phenyl)benzamide;
25 N-(3-((2-amino-5-pyrimidinyl)ethynyl)-5-(trifluoromethyl)phenyl)-3-(trifluoromethyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-(1-methyl-4-piperidinyl)-5-(trifluoromethyl)phenyl)benzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-(trifluoromethyl)phenyl)-2-thiophenecarboxamide;
30 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3-(dimethylamino)propyl)(methylamino)-5-(trifluoromethyl)phenyl)-2-thiophenecarboxamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(4-(1,1-

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- dimethylethyl)phenyl)-4-methylbenzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3-(dimethylamino)propyl)(methyl)amino)-5-(1,1-dimethylethyl)phenyl)-4-methylbenzamide;
5 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3-(dimethylamino)propyl)(methyl)amino)-5-(1,1-dimethylethyl)phenyl)-2-thiophenecarboxamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(3,5-bis(trifluoromethyl)phenyl)-4-methylbenzamide;
10 3-((2-amino-5-pyrimidinyl)ethynyl)-4-chloro-N-(3-(trifluoromethyl)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-chloro-2-((3-(dimethylamino)propyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-4-methylbenzamide;
15 3-((2-amino-5-pyrimidinyl)ethynyl)-4-chloro-N-(3-methyl-4-(1-methylethyl)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-chloro-N-(4-(1,1-dimethylethyl)phenyl)benzamide;
3-((2-amino-4-methyl-5-pyrimidinyl)ethynyl)-N-(2-((3-(dimethylamino)propyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-4-methylbenzamide;
20 3-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3-(dimethylamino)propyl)(methyl)amino)sulfonyl)-5-(trifluoromethyl)phenyl)-4-methylbenzamide;
25 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-(trifluoromethyl)phenyl)-3-thiophenecarboxamide;
5-((2-amino-4-methyl-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(methyl((3R)-1-methyl-3-pyrrolidinyl)amino)-5-(trifluoromethyl)phenyl)benzamide;
30 5-((2-amino-4-methyl-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(methyl((3S)-1-methyl-3-pyrrolidinyl)amino)-5-(trifluoromethyl)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(5-chloro-2-((3-(dimethylamino)propyl)(methyl)amino)phenyl)-4-

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- methylbenzamide;
- 3-((2-amino-5-pyrimidinyl)ethynyl)-N-(4-chloro-3-(trifluoromethyl)phenyl)-4-methylbenzamide;
- 3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-methyl-4-
- 5 (1-methylethyl)phenyl)benzamide;
- 3-((2-amino-5-pyrimidinyl)ethynyl)-5-fluoro-N-(2-(methyl((3S)-1-methyl-3-pyrrolidinyl)amino)-5-(trifluoromethyl)phenyl)benzamide;
- 3-((2-amino-5-pyrimidinyl)ethynyl)-5-fluoro-N-(2-
- 10 (methyl((3R)-1-methyl-3-pyrrolidinyl)amino)-5-(trifluoromethyl)phenyl)benzamide;
- 5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(3-((4-methyl-1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)benzamide;
- 5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(3-((4-methyl-
- 15 1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)benzamide;
- 3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-((4-methyl-1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)benzamide;
- 3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-((4-methyl-1-piperazinyl)carbonyl)-5-(trifluoromethyl)phenyl)benzamide;
- 20 5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(3-((4-methyl-1-piperazinyl)carbonyl)-5-(trifluoromethyl)phenyl)benzamide;
- 3-((2-amino-5-pyrimidinyl)ethynyl)-4-(methyloxy)-N-(2-methyl-3-(trifluoromethyl)phenyl)benzamide;
- 3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(2-((4-methyl-
- 25 1-piperazinyl)sulfonyl)-5-(trifluoromethyl)phenyl)benzamide;
- 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-(1-methyl-4-piperidinyl)-5-(trifluoromethyl)phenyl)-3-thiophenecarboxamide;
- 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-chloro-2-((3-
- 30 (dimethylamino)propyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide;
- 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3-(dimethylamino)propyl)(methyl)amino)sulfonyl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide;

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- 5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-((4-methyl-1-piperazinyl)sulfonyl)-5-(trifluoromethyl)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(2-methyl-3-(trifluoromethyl)phenyl)benzamide;
- 5 3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-((trifluoromethyl)oxy)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-(methyloxy)-N-(3-((trifluoromethyl)oxy)phenyl)benzamide;
- 10 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3-(dimethylamino)propyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-3-thiophenecarboxamide;
4-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3-(dimethylamino)propyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-2-thiophenecarboxamide;
- 15 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-((1,1-dioxido-4-thiomorpholinyl)carbonyl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide;
5-((2-amino-4-methyl-5-pyrimidinyl)ethynyl)-N-(3-chloro-2-((3-(dimethylamino)propyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide;
- 20 5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(1H-1,2,4-triazol-1-yl)-5-(trifluoromethyl)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-((1R)-1-phenylethyl)benzamide;
- 25 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((dimethylamino)methyl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-methyl-5-isoxazolyl)benzamide;
- 30 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(5-cyclopropyl-2-((3-(dimethylamino)propyl)(methyl)amino)phenyl)-2-fluorobenzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-(((2S)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-3-

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- thiophenecarboxamide;
- 3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-((1S)-1-(1,3-thiazol-2-yl)ethyl)benzamide;
- 3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-((1R)-1-(1,3-thiazol-2-yl)ethyl)benzamide;
- 5 3-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-methyl-5-isoxazolyl)-4-(methyloxy)benzamide;
- 3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(2-(4-thiomorpholinyl)-5-(trifluoromethyl)phenyl)benzamide;
- 10 3-((2-amino-5-pyrimidinyl)ethynyl)-N-(3,4-dimethyl-5-isoxazolyl)-4-methylbenzamide;
- 3-((2-amino-5-pyrimidinyl)ethynyl)-N-(3,4-dimethyl-5-isoxazolyl)-4-(methyloxy)benzamide;
- 3-((2-amino-5-pyrimidinyl)ethynyl)-4-(methyloxy)-N-(3-(1-methyl-4-piperidinyl)-5-(trifluoromethyl)phenyl)benzamide;
- 15 5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(methyl((3S)-1-methyl-3-pyrrolidinyl)amino)-5-(trifluoromethyl)phenyl)benzamide;
- 5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(methyl((3R)-1-methyl-3-pyrrolidinyl)amino)-5-(trifluoromethyl)phenyl)benzamide;
- 20 3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-(4-methyl-1-piperazinyl)-5-(trifluoromethyl)phenyl)benzamide;
- 5-((2-amino-5-pyrimidinyl)ethynyl)-2-(methyloxy)-N-(3-(4-methyl-1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)benzamide;
- 25 N-(4-((2-amino-5-pyrimidinyl)ethynyl)-3-methylphenyl)-N'-(3-(trifluoromethyl)phenyl)urea;
- N-(4-((2-amino-5-pyrimidinyl)ethynyl)-3-methylphenyl)-N'-(3-fluorophenyl)urea;
- 30 N-(4-((2-amino-5-pyrimidinyl)ethynyl)-3-methylphenyl)-3-(trifluoromethyl)benzamide;
- N-(4-((2-amino-5-pyrimidinyl)ethynyl)-3-methylphenyl)-4-(trifluoromethyl)benzamide;

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- 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3-(dimethylamino)propyl)(methyl)amino)-5-(trifluoromethyl)phenyl)-2,3-dihydro-1-benzofuran-7-carboxamide;
- 5 4-methyl-N-(3-((4-methyl-1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)-3-(2-quinoxalinylethynyl)benzamide;
- 4-methyl-3-(2-quinoxalinylethynyl)-N-(3-(trifluoromethyl)phenyl)benzamide;
- N-methyl-5-((2-methyl-5-((3-(trifluoromethyl)phenyl)amino)carbonyl)phenyl)ethynyl)-2-pyridinecarboxamide;
- 10 3-(3H-imidazo[4,5-b]pyridin-6-ylethynyl)-4-methyl-N-(3-(trifluoromethyl)phenyl)benzamide;
- 4-methyl-N-(3-(((2S)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-3-(3-quinolinylethynyl)benzamide;
- 15 4-methyl-N-(3-(((2S)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)-3-(2-quinoxalinylethynyl)benzamide;
- N-methyl-5-((2-methyl-5-((3-(((2S)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)amino)carbonyl)phenyl)ethynyl)-2-pyridinecarboxamide;
- 20 3-(3H-imidazo[4,5-b]pyridin-6-ylethynyl)-4-methyl-N-(3-(((2S)-1-methyl-2-pyrrolidinyl)methyl)oxy)-5-(trifluoromethyl)phenyl)benzamide;
- 25 4-methyl-N-(3-((4-methyl-1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)-3-(3-quinolinylethynyl)benzamide;
- 4-methyl-N-(3-((4-methyl-1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)-3-(2-quinoxalinylethynyl)benzamide;
- 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-(methyl((3R)-1-methyl-3-pyrrolidinyl)amino)-5-(trifluoromethyl)phenyl)-2-(methoxy)benzamide;
- 30 N-(4-((2-amino-5-pyrimidinyl)ethynyl)phenyl)-3-(trifluoromethyl)benzamide;
- N-(4-((2-amino-5-pyrimidinyl)ethynyl)phenyl)-1H-

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- benzimidazol-2-amine;
5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3S)-3-(dimethylamino)-1-piperidinyl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide;
- 5 N-(4-((2-amino-5-pyrimidinyl)ethynyl)-1-naphthalenyl)-1H-benzimidazol-2-amine;
5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-(4-(dimethylamino)-1-piperidinyl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(1-piperidinyl)-5-(trifluoromethyl)phenyl)benzamide;
- 10 5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(2-oxo-1-pyrrolidinyl)-5-(trifluoromethyl)phenyl)benzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-2-(methyloxy)-N-(2-(1-piperidinyl)-5-(trifluoromethyl)phenyl)benzamide;
- 15 2-fluoro-5-((2-(methylamino)-5-pyrimidinyl)ethynyl)-N-(2-(methyl((3R)-1-methyl-3-pyrrolidinyl)amino)-5-(trifluoromethyl)phenyl)benzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(4-methyl-1-piperazinyl)-5-(trifluoromethyl)phenyl)benzamide;
- 20 5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(2-oxo-1,3-oxazolidin-3-yl)-5-(trifluoromethyl)phenyl)benzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(3-methyl-2-oxo-1-imidazolidinyl)-5-(trifluoromethyl)phenyl)benzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3R)-3-(dimethylamino)-1-piperidinyl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide;
- 25 5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-((3S)-3-(methylamino)-1-piperidinyl)-5-(trifluoromethyl)phenyl)benzamide;
- 30 N-(2-((3S)-3-amino-1-piperidinyl)-5-(trifluoromethyl)phenyl)-5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluorobenzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(3-oxo-1-piperazinyl)-5-(trifluoromethyl)phenyl)benzamide;

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- 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3R)-3-
((dimethylamino)methyl)-1-pyrrolidinyl)-5-
(trifluoromethyl)phenyl)-2-fluorobenzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-((3R)-3-
5 hydroxy-1-piperidinyl)-5-(trifluoromethyl)phenyl)benzamide;
4-((2-(ethyloxy)phenyl)oxy)-5-(phenylethynyl)-N-(4-((2-(1-
pyrrolidinyl)ethyl)oxy)phenyl)-2-pyrimidinamine;
5-((2,6-dimethylphenyl)ethynyl)-4-((2-(ethyloxy)phenyl)oxy)-
N-(4-((2-(1-pyrrolidinyl)ethyl)oxy)phenyl)-2-pyrimidinamine;
10 5-((2,6-dimethylphenyl)ethynyl)-4-((2-(ethyloxy)phenyl)oxy)-
N-(4-(4-methyl-1-piperazinyl)phenyl)-2-pyrimidinamine;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(4-((2-
(dimethylamino)ethyl)oxy)phenyl)-4-methylbenzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(4-
15 (trifluoromethyl)-2-pyridinyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-fluoro-5-
(trifluoromethyl)phenyl)-4-methylbenzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(2-
(methyloxy)-5-(trifluoromethyl)phenyl)benzamide;
20 3-((2-amino-5-pyrimidinyl)ethynyl)-N-(4-ethyl-2-pyridinyl)-
4-methylbenzamide;
4-methyl-3-((2-((2-(4-morpholinyl)ethyl)amino)-5-
pyrimidinyl)ethynyl)-N-(3-(trifluoromethyl)phenyl)benzamide;
4-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-fluoro-5-
25 (trifluoromethyl)phenyl)-3-methylbenzamide;
4-methyl-3-((2-((4-(4-methyl-1-piperazinyl)phenyl)amino)-5-
pyrimidinyl)ethynyl)-N-(3-(trifluoromethyl)phenyl)benzamide;
3-((6-amino-3-pyridinyl)ethynyl)-4-methyl-N-(3-
(trifluoromethyl)phenyl)benzamide;
30 3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(4-(4-(1-
methylethyl)-1-piperazinyl)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(4-(1,1-dimethylethyl)-
3-((N,N-dimethylglycyl)amino)phenyl)-4-methylbenzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(5,5-dimethyl-3-oxo-1-

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- cyclohexen-1-yl)-4-methylbenzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-(1,1-dimethylethyl)-
1-methyl-1H-pyrazol-5-yl)-4-methylbenzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(5-(1,1-dimethylethyl)-
5 2-(methyloxy)phenyl)-4-methylbenzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-
((dimethylamino)methyl)-5-(trifluoromethyl)phenyl)-4-
methylbenzamide;
4-((2-amino-5-pyrimidinyl)ethynyl)-3-methyl-N-(3-((4-methyl-
10 1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-(2-oxo-1-
pyrrolidinyl)-5-(trifluoromethyl)phenyl)benzamide;
N-(3-((2-amino-5-pyrimidinyl)ethynyl)-2-methylphenyl)-3-
(trifluoromethyl)benzamide;
15 3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-(1-
pyrrolidinylmethyl)-5-(trifluoromethyl)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-(4-
morpholinylmethyl)-5-(trifluoromethyl)phenyl)benzamide;
3-((2-amino-4-methyl-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-
20 ((4-methyl-1-piperazinyl)methyl)-5-
(trifluoromethyl)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(2-(2-oxo-1-
pyrrolidinyl)-5-(trifluoromethyl)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(2-(2-oxo-1,3-
25 oxazolidin-3-yl)-5-(trifluoromethyl)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(4-cyano-2-pyridinyl)-
4-methylbenzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-(3-(4-
morpholinyl)propyl)-5-(trifluoromethyl)phenyl)benzamide;
30 4-methyl-3-((2-(methylamino)-5-pyrimidinyl)ethynyl)-N-(3-
((4-methyl-1-piperazinyl)methyl)-5-
(trifluoromethyl)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-4-methyl-N-(3-(3-(4-
methyl-1-piperazinyl)propyl)-5-

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- (trifluoromethyl)phenyl)benzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(3-(3-(dimethylamino)-1-propyn-1-yl)-5-(trifluoromethyl)phenyl)-4-methylbenzamide;
3-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-(3-(dimethylamino)-1-propyn-1-yl)-5-(trifluoromethyl)phenyl)-4-methylbenzamide;
5 N-(3-((2-amino-5-pyrimidinyl)ethynyl)-4-methylphenyl)-3-(trifluoromethyl)benzamide;
4-methyl-N-(3-((4-methyl-1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)-3-(3-pyridinylethynyl)benzamide;
10 4-methyl-3-((2-(methylamino)-5-pyrimidinyl)ethynyl)-N-(3-(1-methyl-4-piperidinyl)-5-(trifluoromethyl)phenyl)benzamide;
4-methyl-N-(2-(2-oxo-1-pyrrolidinyl)-5-(trifluoromethyl)phenyl)-3-(3-pyridinylethynyl)benzamide;
4-methyl-3-((2-(methylamino)-4-(2-thienyl)-5-pyrimidinyl)ethynyl)-N-(3-((4-methyl-1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)benzamide;
15 4-methyl-3-((2-((1-methylethyl)amino)-5-pyrimidinyl)ethynyl)-N-(3-((4-methyl-1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)benzamide;
20 4-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-(methyl((3R)-1-methyl-3-pyrrolidinyl)amino)-5-(trifluoromethyl)phenyl)-1-(methyloxy)-2-naphthalenecarboxamide;
4-methyl-3-((4-((2-(methyloxy)phenyl)oxy)-2-((4-(4-methyl-1-piperazinyl)phenyl)amino)-5-pyrimidinyl)ethynyl)-N-(3-(trifluoromethyl)phenyl)benzamide;
25 4-((2-(methyloxy)phenyl)oxy)-N-(4-(4-methyl-1-piperazinyl)phenyl)-5-(phenylethynyl)-2-pyrimidinamine;
N-(3-methyl-4-((4-((2-(methyloxy)phenyl)oxy)-2-((4-(4-methyl-1-piperazinyl)phenyl)amino)-5-pyrimidinyl)ethynyl)phenyl)-N'-(3-(trifluoromethyl)phenyl)urea;
30 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-(3,3-dimethyl-2-oxo-1-azetidyl)-5-(trifluoromethyl)phenyl)-2-(methyloxy)benzamide;

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- 5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(4-thiomorpholinyl)-5-(trifluoromethyl)phenyl)benzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(methyl(1-methyl-4-piperidinyl)amino)-5-(trifluoromethyl)phenyl)benzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-((4-methyl-1-piperazinyl)methyl)-5-(trifluoromethyl)phenyl)benzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-(4-morpholinyl)-5-(trifluoromethyl)phenyl)benzamide;
10 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3S)-3-(dimethylamino)-1-pyrrolidinyl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-((2-(4-morpholinyl)ethyl)oxy)-5-(trifluoromethyl)phenyl)benzamide;
15 5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-((1S,4R)-5-methyl-2,5-diazabicyclo[2.2.1]hept-2-yl)-5-(trifluoromethyl)phenyl)benzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-2-fluoro-N-(2-((2-(1-pyrrolidinyl)ethyl)oxy)-5-(trifluoromethyl)phenyl)benzamide;
20 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3S)-1-ethyl-3-pyrrolidinyl)oxy)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide;
5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3S)-1-ethyl-3-piperidinyl)oxy)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide;
25 5-((2-amino-5-pyrimidinyl)ethynyl)-N-(2-((3S)-3-(dimethylamino)-1-piperidinyl)-5-(trifluoromethyl)phenyl)-2-fluoro-5-((2-(methylamino)-5-pyrimidinyl)ethynyl)benzamide;
5-((2-amino-4-methyl-5-pyrimidinyl)ethynyl)-N-(2-((3S)-3-(dimethylamino)-1-piperidinyl)-5-(trifluoromethyl)phenyl)-2-fluorobenzamide;
30 N-cyclopropyl-4-methyl-3-((2-((2-(4-morpholinyl)ethyl)amino)-5-pyrimidinyl)ethynyl)benzamide;
N-cyclopropyl-4-methyl-3-((6-((2-(4-

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morpholinyl)ethynyl)amino)-3-pyridinyl)ethynyl)benzamide;
N-(4-((2-((4-(4-methyl-1-piperazinyl)phenyl)amino)-5-
pyrimidinyl)ethynyl)phenyl)-1H-benzimidazol-2-amine;
N-(4-((2-((4-(4-methyl-1-piperazinyl)phenyl)amino)-5-
5 pyrimidinyl)ethynyl)phenyl)-3-(trifluoromethyl)benzamide;
4-((2-((4-(4-methyl-1-piperazinyl)phenyl)amino)-5-
pyrimidinyl)ethynyl)-N-(3-(trifluoromethyl)phenyl)benzamide;
and
N-(4-((2-amino-5-pyrimidinyl)ethynyl)phenyl)-2-
10 (phenylamino)benzamide.

19. A pharmaceutical composition comprising a
pharmaceutically acceptable carrier and a compound according
to any of Claims 1-18.

15

20. A method of modulating a protein kinase enzyme in a
subject, the method comprising administering to the subject
an effective dosage amount of a compound according to any of
Claims 1-18.

20

21. The method of Claim 20 wherein the protein kinase
enzyme modulated is Lck or Tie-2.

22. A method of treating a disorder related to at least
25 one of Tie-2 and Lck in a subject, the method comprising
administering to the subject an effective dosage amount of a
compound according to any of Claims 1-18.

23. A method of treating a proliferation-related disorder
30 in a subject, the method comprising administering to the
subject an effective dosage amount of a compound according
to any of Claims 1-18.

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24. The method of Claim 23 wherein the disorder is selected from the group consisting of myocardial infarction, coronary artery disease, peripheral vascular disease, stroke, ocular neovascularization, retinopathy, diabetic
5 retinopathy, age-related macular degeneration, psoriasis, hemangioblastoma, hemangioma, arteriosclerosis, inflammatory disease rheumatoid arthritis, asthma, arterial or post-transplantational atherosclerosis, endometriosis, leukemia and combinations thereof.
- 10
25. A method of treating cancer in a subject, the method comprising administering to the subject an effective dosage amount of a compound according to any of Claims 1-18.
- 15
26. The method of claim 25 wherein administering the effective amount of the compound to the subject comprises administering the compound in combination with one or more compounds selected from antineoplastic agents, anti-angiogenic agents, chemotherapeutic agents and peptidal
20 cancer therapy agents.
27. The method of claim 26 wherein the antineoplastic agents are selected from antibiotic-type agents, alkylating agents, antimetabolite agents, hormonal agents,
25 immunological agents, interferon-type agents, kinase inhibitors, miscellaneous agents and combinations thereof.
28. A method of treating cancer in a subject, the method comprising administering to the subject a pharmaceutical
30 composition comprising an effective dosage amount of a compound according to any of Claims 1-18.

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29. A method of treating angiogenesis in a subject, the method comprising administering to the subject an effective dosage amount of a compound according to any of Claims 1-18.
- 5 30. A method of treating angiogenesis in a subject, the method comprising administering to the subject a pharmaceutical composition comprising an effective dosage amount of a compound according to any of Claims 1-18.
- 10 31. A method of reducing blood flow in a tumor in a subject, said method comprising administering to the subject an effective dosage amount of a compound according to any of claims 1-18.
- 15 32. A method of reducing tumor size in a subject, said method comprising administering to the subject an effective dosage amount of a compound according to any of claims 1-18.
- 20 33. A method of treating inflammation in a subject, the method comprising administering to the subject an effective dosage amount of a compound according to any of Claims 1-18.
- 25 34. A method of treating inflammation in a subject, the method comprising administering to the subject a pharmaceutical composition comprising an effective dosage amount of a compound according to any of Claims 1-18.
- 30 35. A method of inhibiting T cell activation and proliferation in a subject, the method comprising administering to the subject an effective dosage amount of a compound according to any of Claims 1-18.
36. A method of treating arthritis, rheumatoid arthritis, psoriatic arthritis, or osteoarthritis in a subject, the

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method comprising administering to the subject an effective dosage amount of a compound according to any of Claims 1-18.

37. A method of treating organ transplant, acute transplant
5 or heterograft or homograft rejection, or transplantation tolerance induction in a subject, the method comprising administering to the subject an effective dosage amount of a compound according to any of Claims 1-18.

10 36. A method of treating ischemic or reperfusion injury, myocardial infarction, or stroke in a subject, the method comprising administering to the subject an effective dosage amount of a compound according to any of Claims 1-18.

15 39. A method of treating multiple sclerosis, inflammatory bowel disease, including ulcerative colitis, Crohn's disease, lupus, contact hypersensitivity, delayed-type hypersensitivity, and gluten-sensitive enteropathy, type 1
20 diabetes, psoriasis, contact dermatitis, Hashimoto's thyroiditis, Sjogren's syndrome, autoimmune hyperthyroidism, Addison's disease, autoimmune polyglandular disease, autoimmune alopecia, pernicious anemia, vitiligo, autoimmune hypopituitarism, Guillain-Barre syndrome, glomerulonephritis, serum sickness, urticaria, allergic
25 diseases, asthma, hayfever, allergic rhinitis, scleroderma, mycosis fungoides, dermatomyositis, alopecia areata, chronic actinic dermatitis, eczema, Behcet's disease, Pustulosis palmoplantis, Pyoderma gangrenosum, Sezary's syndrome, atopic dermatitis, systemic sclerosis, morphea or atopic
30 dermatitis in a subject, the method comprising administering to the subject an effective dosage amount of a compound according to any of Claims 1-18.

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40. A method of treating colon carcinoma or thymoma in a subject, the method comprising administering to the subject an effective dosage amount of a compound according to any of Claims 1-18.

5

41. The manufacture of a medicament comprising a compound according to any of Claims 1-18.

42. The manufacture of a medicament for the treatment of inflammation or cancer, the medicament comprising an effective dosage amount of a compound according to any of Claims 1-18.

10

43. The manufacture of a medicament for the inhibition of T cell activation and proliferation in a subject, the medicament comprising an effective dosage amount of a compound according to any of Claims 1-18.

15

44. The manufacture of a medicament for the treatment of arthritis, rheumatoid arthritis, psoriatic arthritis, or osteoarthritis in a subject, the medicament comprising an effective dosage amount of a compound according to any of Claims 1-18.

20

45. The manufacture of a medicament for the treatment of organ transplant, acute transplant or heterograft or homograft rejection, or transplantation tolerance induction in a subject, the medicament comprising an effective dosage amount of a compound according to any of Claims 1-18.

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46. The manufacture of a medicament for the treatment of ischemic or reperfusion injury, myocardial infarction, or stroke in a subject, the medicament comprising an effective dosage amount of a compound according to any of Claims 1-18.

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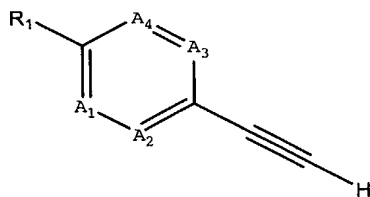
47. The manufacture of a medicament for the treatment of multiple sclerosis, inflammatory bowel disease, including ulcerative colitis, Crohn's disease, lupus, contact hypersensitivity, delayed-type hypersensitivity, and gluten-sensitive enteropathy, type 1 diabetes, psoriasis, contact dermatitis, Hashimoto's thyroiditis, Sjogren's syndrome, autoimmune hyperthyroidism, Addison's disease, autoimmune polyglandular disease, autoimmune alopecia, pernicious anemia, vitiligo, autoimmune hypopituitarism, Guillain-Barre syndrome, glomerulonephritis, serum sickness, urticaria, allergic diseases, asthma, hayfever, allergic rhinitis, scleroderma, mycosis fungoides, dermatomyositis, alopecia areata, chronic actinic dermatitis, eczema, Behcet's disease, Pustulosis palmoplantis, Pyoderma gangrenosum, Sezary's syndrome, atopic dermatitis, systemic sclerosis, morphea or atopic dermatitis in a subject comprising an effective dosage amount of a compound according to any of Claims 1-18.

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48. The manufacture of a medicament for the treatment of colon carcinoma or thymoma in a subject comprising an effective dosage amount of a compound according to any of Claims 1-18.

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49. A process of making a compound of Formula I, the process comprising the steps of
reacting a compound of Formula A,



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A

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wherein A^1 , A^2 , A^3 , A^4 and R^1 are as defined in Claim 1, with a compound of Formula B, $X-R^2$ wherein X is a halogen selected from bromine and iodine and R^2 is as defined in claim 1, to form a compound of formula I.

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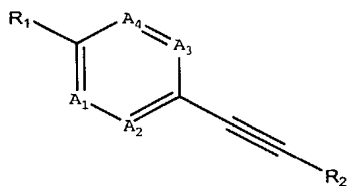
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ance Notes on Codes and Abbreviations" appearing at the begin-
ning of each regular issue of the PCT Gazette.*

(54) Title: HETEROARYL-SUBSTITUTED ALKYNE COMPOUNDS AND METHOD OF USE



(I)

(57) Abstract: The present invention comprises a new class of compounds useful for the prophylaxis and treatment of protein kinase mediated diseases, including inflammation, cancer and related conditions. The compounds have a general Formula I: wherein A1, A2, A3, A4, R1 and R2 are defined herein. Accordingly, the invention also comprises pharmaceutical compositions comprising the compounds of the invention, methods for the prophylaxis and treatment of kinase mediated diseases using the compounds and compositions of the invention, and intermediates and processes useful for the preparation of compounds of the invention.

INTERNATIONAL SEARCH REPORT

International application No
PCT/US2005/037299

A. CLASSIFICATION OF SUBJECT MATTER INV. C07D239/42 A61K31/505 A61P35/00		
According to International Patent Classification (IPC) or to both national classification and IPC		
B. FIELDS SEARCHED Minimum documentation searched (classification system followed by classification symbols) C07D Documentation searched other than minimum documentation to the extent that such documents are included in the fields searched		
Electronic data base consulted during the international search (name of data base and, where practical, search terms used) EPO-Internal, BEILSTEIN Data, WPI Data, PAJ		
C. DOCUMENTS CONSIDERED TO BE RELEVANT		
Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
X	WO 01/53274 A (AGOURON PHARMACEUTICALS, INC) 26 July 2001 (2001-07-26) pages 188,197	1,17,49
Y	-----	1-49
X	WO 2004/062601 A (CHIRON CORPORATION; ANDERSON, NEILS, H; BOWMAN, JASON; ERWIN, ALICE; H) 29 July 2004 (2004-07-29) p. 211,253,256	1-15,19,41,49
P,X	WO 2004/112714 A (SMITHKLINE BEECHAM CORPORATION; BADIANG, JENNIFER, G; DICKERSON, SCOTT) 29 December 2004 (2004-12-29) the whole document ----- -/--	1-49
<input checked="" type="checkbox"/> Further documents are listed in the continuation of Box C. <input checked="" type="checkbox"/> See patent family annex.		
* Special categories of cited documents : *A* document defining the general state of the art which is not considered to be of particular relevance *E* earlier document but published on or after the international filing date *L* document which may throw doubts on priority claim(s) or which is cited to establish the publication date of another citation or other special reason (as specified) *O* document referring to an oral disclosure, use, exhibition or other means *P* document published prior to the international filing date but later than the priority date claimed *T* later document published after the international filing date or priority date and not in conflict with the application but cited to understand the principle or theory underlying the invention *X* document of particular relevance; the claimed invention cannot be considered novel or cannot be considered to involve an inventive step when the document is taken alone *Y* document of particular relevance; the claimed invention cannot be considered to involve an inventive step when the document is combined with one or more other such documents, such combination being obvious to a person skilled in the art. *G* document member of the same patent family		
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Name and mailing address of the ISA/ European Patent Office, P.B. 5818 Patentlaan 2 NL - 2280 HV Rijswijk Tel. (+31-70) 340-2040, Tx. 31 651 epo nl, Fax: (+31-70) 340-3016		Authorized officer Zellner, A

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C(Continuation). DOCUMENTS CONSIDERED TO BE RELEVANT

Category*	Citation of document, with indication, where appropriate, of the relevant passages	Relevant to claim No.
P,X	WO 2005/060969 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; JONES, CLIFFORD, DAVID; LUKE,) 7 July 2005 (2005-07-07) the whole document -----	1-49
P,X	WO 2005/060970 A (ASTRAZENECA AB; ASTRAZENECA UK LIMITED; JONES, CLIFFORD, DAVID; LUKE,) 7 July 2005 (2005-07-07) the whole document -----	1-49
P,X	WO 2005/016914 A (SMITHKLINE BEECHAM CORPORATION; RENO, MICHAEL, JOHN; STEVENS, KIRK, LA) 24 February 2005 (2005-02-24) the whole document -----	1-49
E	WO 2005/117867 A (BRISTOL-MYERS SQUIBB COMPANY; BORZILLERI, ROBERT M; CORNELIUS, LYNDON) 15 December 2005 (2005-12-15) the whole document -----	1-49
E	WO 2006/004532 A (ASTRAZENECA AB; GABOS, BALINT; RIPA, LENA; STENVALL, KRISTINA) 12 January 2006 (2006-01-12) the whole document -----	1-49
A	WO 01/60816 A (AMGEN INC) 23 August 2001 (2001-08-23) the whole document -----	1-49
P,A	WO 2004/094379 A (AMGEN INC) 4 November 2004 (2004-11-04) the whole document -----	1-49
Y	CONDE, J.J.; ET AL.: TETRAHEDRON LETTERS, vol. 41, 2000, pages 811-814, XP002372776 the whole document -----	1-49

INTERNATIONAL SEARCH REPORT

International application No.
PCT/US2005/037299

Box II Observations where certain claims were found unsearchable (Continuation of item 2 of first sheet)

This International Search Report has not been established in respect of certain claims under Article 17(2)(a) for the following reasons:

1. ☒ Claims Nos.:
because they relate to subject matter not required to be searched by this Authority, namely:

Although claims 20-40 are directed to a method of treatment of the human/animal body, the search has been carried out and based on the alleged effects of the compound/composition.
2. ☐ Claims Nos.:
because they relate to parts of the International Application that do not comply with the prescribed requirements to such an extent that no meaningful International Search can be carried out, specifically:
3. ☐ Claims Nos.:
because they are dependent claims and are not drafted in accordance with the second and third sentences of Rule 6.4(a).

Box III Observations where unity of invention is lacking (Continuation of item 3 of first sheet)

This International Searching Authority found multiple inventions in this international application, as follows:

1. ☐ As all required additional search fees were timely paid by the applicant, this International Search Report covers all searchable claims.
2. ☐ As all searchable claims could be searched without effort justifying an additional fee, this Authority did not invite payment of any additional fee.
3. ☐ As only some of the required additional search fees were timely paid by the applicant, this International Search Report covers only those claims for which fees were paid, specifically claims Nos.:
4. ☐ No required additional search fees were timely paid by the applicant. Consequently, this International Search Report is restricted to the invention first mentioned in the claims; it is covered by claims Nos.:

Remark on Protest

- ☐ The additional search fees were accompanied by the applicant's protest.
- ☐ No protest accompanied the payment of additional search fees.

INTERNATIONAL SEARCH REPORT

 International application No
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Patent document cited in search report		Publication date	Patent family member(s)	Publication date
WO 0153274	A	26-07-2001	AU 3448401 A	31-07-2001
			BR 0108025 A	05-11-2002
			CA 2394703 A1	26-07-2001
			EP 1252146 A1	30-10-2002
			JP 2003529558 T	07-10-2003
			MX PA02007102 A	28-01-2003
WO 2004062601	A	29-07-2004	AU 2004204760 A1	29-07-2004
			CA 2512582 A1	29-07-2004
			EP 1618087 A2	25-01-2006
WO 2004112714	A	29-12-2004	NONE	
WO 2005060969	A	07-07-2005	NONE	
WO 2005060970	A	07-07-2005	NONE	
WO 2005016914	A	24-02-2005	NONE	
WO 2005117867	A	15-12-2005	US 2005245530 A1	03-11-2005
WO 2006004532	A	12-01-2006	NONE	
WO 0160816	A	23-08-2001	AU 3704101 A	27-08-2001
			CA 2400447 A1	23-08-2001
			CN 1429222 A	09-07-2003
			HU 0301117 A2	29-12-2003
			ZA 200206386 A	26-11-2003
WO 2004094379	A	04-11-2004	EP 1628665 A2	01-03-2006